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THE USE OF ANTITHYROID DRUGS DURING PREGNANCY*†

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RECENT studies have indicated that pregnancy with concurrent hyperthyroidism is not more frequent than might be expected from the chance co-existence of the two conditions. For many years the association was regarded as serious, but as treatment for hyperthyroidism has become more effective, there has been less cause for alarm. On the basis of a review of published cases, Gardner-Hill (1) concluded in 1929 that one half of pregnancies with concurrent hyperthyroidism ended unsuccessfully. Over the past thirty years, however, other reports (2–5) on the treatment of hyperthyroidism during pregnancy with Lugol's solution, with or without subtotal thyroidectomy, have indicated that the incidence of miscarriage and stillbirth is reduced by therapy but remains higher in thyrotoxic than in normal patients. In the most recent report on this subject

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(6), the hyperthyroidism was treated with antithyroid drugs followed by thyroidectomy but the incidence of fetal loss was still 33 per cent.

The problem of therapy is complicated by the fact that over-treatment and consequent hypothyroidism can also lead to obstetric difficulties. It would appear that hypothyroidism is most apt to lead to fetal loss if it occurs early in pregnancy, whereas myxedema late in pregnancy is not inconsistent with a normal outcome. In the latter case, however, compensatory enlargement of the fetal thyroid may occur, at least under certain circumstances.

Radioactive iodine has not been widely used during pregnancy because of the findings of Chapman, Corner, and Robinson (7) that after the third month the fetal thyroid collects significant amounts of radioiodine. However, patients treated for hyperthyroidism with radioiodine before pregnancy have subsequently carried through pregnancy in a normal way and Hertz (8) has recorded 11 such cases.

Antithyroid drugs have not been widely used during pregnancy. Isolated instances of goiter in the newborn infant have been recorded (9, 10), pointing to the importance of avoiding overdosage. Congenital anomalies have also been described after antithyroid therapy as well as after iodine or thyroidectomy but, as noted below, there is no reason to believe that the treatment was responsible. Most reports to date have recorded a normal outcome of the pregnancy when antithyroid therapy was used (3, 11, 12, 13, 14).

The use of antithyroid drugs during pregnancy involves a consideration of the effect of these compounds upon the fetal thyroid. Animal experiments have clearly shown that the administration of antithyroid compounds during pregnancy can bring about compensatory thyroid enlargement in the fetus as well as in the mother. It is well recognized that the administration of adequate doses of antithyroid compounds to the normal animal or to the normal human being can induce a state of myxedema in association with goiter. However, when hyperthyroidism is treated with an antithyroid drug, the dosage is so adjusted as to bring about a state of euthyroidism and when this is done, enlargement of the thyroid does not usually occur. As the dose of antithyroid drug used to restore the hypermetabolism of thyrotoxicosis to normal still permits the thyroid gland to form and to secrete a normal amount of thyroid hormone, there is reason to suppose that the fetal thyroid would not be significantly suppressed by appropriate treatment of the thyrotoxic mother. Furthermore, though the commonly employed antithyroid drugs can be shown to traverse the placenta, it is probable that the fetus is exposed to a lesser concentration than is the mother.

CLINICAL MATERIAL AND METHODS

This study is based upon observations made over the course of six years on 19 patients who were pregnant during or shortly after antithyroid therapy for hyperthyroidism. There was no selection of the patients, as all were treated routinely with antithyroid drugs. They were seen at intervals of four to six weeks and the dosage adjusted on the basis of the response as judged by clinical criteria.

Most of the patients were treated with propylthiouracil; the usual dosage of 100 milligrams every eight hours was used. When the patients were considered to be euthyroid, the dosage was reduced to 50 milligrams every eight hours. In most instances, the smaller dose was given during the latter half of gestation and usually treatment was stopped at parturition. In 13 instances, propylthiouracil alone was used; in 1, mercaptoimidazole was employed in a maximal dose of 100 milligrams once daily; in 2, methylmercaptoimidazole (15) was used in a dose of 5 milligrams every eight hours; and 3 patients first received propylthiouracil and later methylmercaptoimidazole.[1] These dosages completely controlled the hyperthyroidism and in no instance was frank hypothyroidism induced during pregnancy. There were no side effects. No iodine was used during or after therapy with the antithyroid compound, and thyroid was prescribed in only 1 instance during pregnancy.

CLINICAL FINDINGS

The pertinent observations made on this series of 19 patients are shown in diagrammatic form in Figure 1. It is to be noted that the onset of hyperthyroidism in Patients 1 to 4 preceded the time covered by the diagram, the disease having had its onset in 1938, 1941, 1941, and 1942, respectively. In 3 instances (Patients 1, 4, and 5), thyroidectomy had been performed without avail, and these patients had received iodine intermittently since the operations. Included in the diagram are 6 pregnancies which were completed before the patients first presented themselves for treatment and information about these pregnancies was obtained by history alone. In 25 instances pregnancy occurred either during or after treatment with the antithyroid compounds and 3 of these pregnancies have not yet been completed. As shown in Table 1, all 22 children were born alive and lived. There were 10 females and 12 males. In no instance was the infant noted to have a goiter, and there were no symptoms or signs of any thyroid disturbance. As far as could be ascertained from the

[1] The propylthiouracil and mercaptoimidazole were provided for this study by the Lederle Laboratories Division of the American Cyanamid Company, and the methylmercaptoimidazole ("Tapazole") by Eli Lilly and Company.

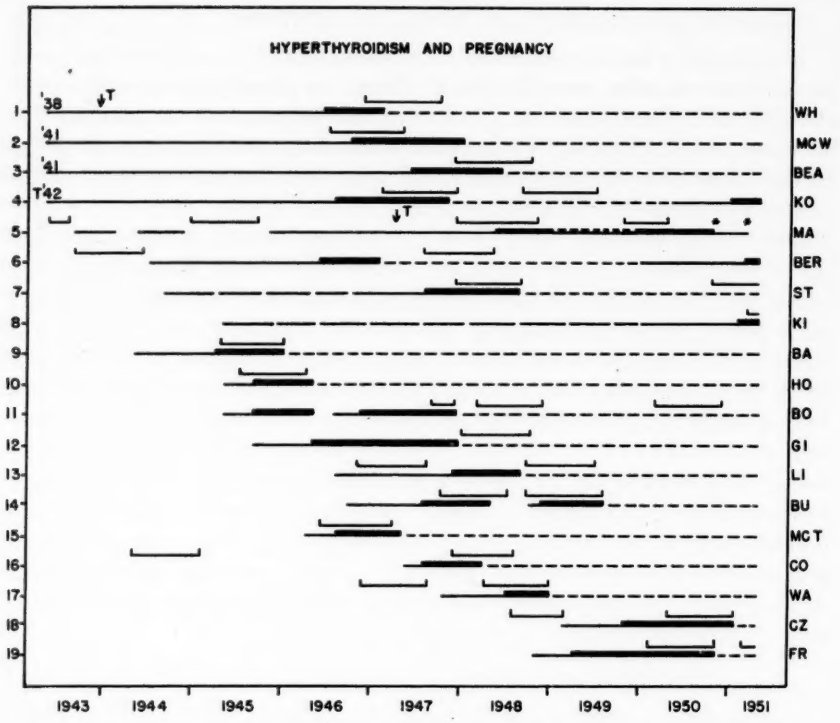

FIG. 1. Diagrammatic representation of the course of hyperthyroidism and its treatment in 19 patients and 31 pregnancies. In each case the solid base-line on the left denotes the duration of hyperthyroidism before treatment, and when this line is shown as long dashes it implies that there was some uncertainty as to whether or not hyperthyroidism was present. The heavy black bars show the periods of antithyroid drug therapy and the short-dashed lines to the right indicate the interval of complete remission of hyperthyroidism after stopping treatment. The periods of pregnancy are shown by the bracketed lines above. The arrows labeled T indicate subtotal thyroidectomy (Cases 1, 4, and 5) and the two asterisks (Case 5) indicate therapeutic doses of radioiodine.

obstetrician, the pediatrician, and from subsequent examination, there were no abnormalities of development which could possibly have been related to any disturbance in function of the fetal thyroid. In 3 instances the pregnancies terminated prematurely. In the case of Patient No. 2, there was severe hyperthyroidism during the first three months of pregnancy before treatment was instituted. Though the thyrotoxicosis was controlled within a month, parturition took place seven and one-half months after the last menstrual period and the baby, weighing only two pounds at birth, had to be given premature-infant care in the hospital for

three months. Its subsequent development was normal, however. Another premature delivery at six months occurred in the case of patient No. 5. Propylthiouracil therapy had been given during a preceding pregnancy, but owing to intermittent and irregular dosage, she was severely thyrotoxic during the first three months. Though brought under control by larger dosage thereafter, she delivered at six months a four and one-half pound baby, which was normal at birth and developed normally thereafter. Parturition was preceded by a premature rupture of the membranes and hemorrhage. The breech delivery was a difficult one and associated with

TABLE 1. THE LENGTHS OF GESTATION IN 19 PATIENTS WITH HYPERTHYROIDISM TREATED WITH ANTITHYROID DRUGS AND THE WEIGHTS OF THE 22 CHILDREN BORN DURING OR AFTER THERAPY

No.	Pt.	Gestation (mos.)	Child				Thyroid status of mother during pregnancy*
			Condition	Sex & birth wt.			
					lb.	*oz.*	
1	Wh	9	normal	F	9	4	Euthyroid
2	McW	7½	premature	M	2		Severely thyrotoxic first 3 mos.
3	Bea	9	normal	F	6	9	Euthyroid
4 (a)	Ko	9	normal	M	6	6	Euthyroid
(b)		9	clubfeet	F	7	14½	Mildly thyrotoxic (untreated)
5 (a)	Ma	9	normal	F	8	14	Mildly thyrotoxic
(b)		6	premature	M	4	8	Severely thyrotoxic first 5 mos.
6	Ber	9	normal	F	7	13	Euthyroid (after treatment)
7 (a)	St	9	normal	F	8	4½	Euthyroid
(b)		—	undelivered	—	—	—	Euthyroid (after treatment)
8	Ki	—	undelivered	—	—	—	Euthyroid
9	Ba	9	normal	F	6	12	Euthyroid
10	Ho	9	normal	F	7	12	Euthyroid
11 (a)	Bo	9	normal	F	7	3	Euthyroid (after treatment)
(b)		9	normal	M	7	8	Euthyroid (after treatment)
12	Gi	9	normal	M	6	10	Euthyroid (after treatment)
13	Li	9½	normal	F	7	6	Euthyroid (after treatment)
14 (a)	Bu	9	normal	M	7	12	Euthyroid
(b)		9	normal	M	7	13	Euthyroid
15	McT	9	normal	M	6	13	Thyrotoxic first 3 mos.
16	Co	8	normal	M	4	10	Euthyroid
17	Wa	9	normal	M	10		Thyrotoxic first 4 mos.
18	Cz	9	normal	M	7	1	Euthyroid
19 (a)	Fr	9	normal	M	8	2	Euthyroid
(b)		—	undelivered	—	—	—	Euthyroid (after treatment)

* Unless otherwise stated, the mothers received antithyroid therapy during pregnancy.

further hemorrhage. The mother recovered completely, however. Patient No. 16 was euthyroid throughout pregnancy and delivered at the end of eight months a four-pound ten-ounce baby without incident.

In all other instances the pregnancy terminated approximately nine months after the last normal menstrual period. The second child born to patient No. 4 had bilateral clubfeet. The patient received no therapy during this pregnancy, though subsequent inquiry indicated that hyperthyroidism may have returned before then. The previous pregnancy, which was completed shortly after the first course of propylthiouracil, was entirely normal.

TABLE 2. THE ONSET OF HYPERTHYROIDISM IN RELATION TO PREGNANCY AND PARTURITION

	No. of patients
During pregnancy	0
After delivery	5
Following miscarriage	2
While not pregnant	12
Total	19

Onset of hyperthyroidism in relation to pregnancy

Some older observations have suggested that both simple goiter and hyperthyroidism often make their appearance for the first time during pregnancy. Although this may be the case in the instance of simple goiter, more recent studies indicate that hyperthyroidism rarely starts during pregnancy (16). The latter view is supported by the findings reported here (Table 2). In no instance did it appear probable that the thyrotoxicosis had its onset during pregnancy. In 1 case (No. 14) a relapse seemed to have occurred coincident with the beginning of a second pregnancy but the interval between the two pregnancies was so short (two months) that is was difficult to be sure whether a true remission of the disease had been achieved.

In 5 instances the hyperthyroidism seemed to have started shortly after delivery, and in 2 cases it appeared to have had its onset following miscarriage. In the majority (12 cases) the onset of the hyperthyroidism bore no relation to gestation.

Hyperthyroidism and disturbances of reproductive function

Hyperthyroidism has long been cited as one of the causes of menstrual abnormalities, and it has been observed (16) that fertility in the female is

impaired by hyperthyroidism. Support for these views was provided by the finding that 10 of the 19 patients studied exhibited some disturbance in reproductive function in association with hyperthyroidism.

As may be seen in Table 3, symptoms of hyperthyroidism dated from miscarriage or death of a newborn infant in 4 instances (Nos. 5, 13, 17, and 18). In 2 of these, the infant was known to have been congenitally malformed. Though these upsetting events may be surmised to have been precipitating factors in the onset of the hyperthyroidism, it is still possible that the hyperthyroidism may have antedated the obstetric difficulties and contributed to them. In any event the patients dated the onset of

TABLE 3. REPRODUCTIVE DISTURBANCES NOTED IN 10 OF THE 19 PATIENTS BEFORE TREATMENT OF THE HYPERTHYROIDISM

No.	Pt.	
1.	Wh	Cycles normal. No pregnancies for 7 years.
2.	McW	Cycles normal. Married 6 years. No children.
5.	Ma	Miscarriage before onset of symptoms.
7.	St	Thyroid therapy for irregular cycles. Miscarriage.
8.	Ki	Cycles normal. Married 7 years. No children.
11.	Bo	Functional bleeding treated with progesterone.
13.	Li	Irregular cycles. Term-infant died; spina bifida.
16.	Co	Thyroid therapy for irregular cycles.
17.	Wa	Death of newborn infant before onset of symptoms.
18.	Cz	Miscarriage before onset of symptoms.

hyperthyroidism to the loss of the infant in Cases 17 and 18, whereas in Case 13 thyrotoxicosis clearly preceded the death of the newborn.

Failure to conceive had been a major difficulty in 3 cases (Nos. 1, 2, and 8). Patient No. 1 had suffered mild hyperthyroidism since the birth of her only child seven years previously. Subtotal thyroidectomy had been unsuccessful and intermittent iodide therapy had been only partially effective. Six months after treatment with propylthiouracil had been instituted, she conceived and in due course bore a normal child. Patient No. 8 had been married seven years and careful and repeated studies of her husband and herself had failed to disclose a cause for sterility. Moderately severe hyperthyroidism had clearly been present for a period of two years and milder symptoms dated from the time of marriage. All symptoms and signs of hyperthyroidism were dispelled by four weeks' treatment with methylmercaptoimidazole and conception occurred two weeks later. Patient No. 2 when first seen was severely hyperthyroid and a thyrotoxic crisis seemed imminent. She had conceived three months before, after six years of a childless marriage. Three of the patients (Nos. 7, 13, and 16)

had been under the care of their physicians because of irregular menstrual cycles and, interestingly enough, 2 of them had exhibited signs of hypothyroidism. They were being treated with thyroid when the symptoms of hyperthyroidism first began.

One instance of severe functional uterine bleeding was encountered during hyperthyroidism. This patient (No. 11) was inadequately treated with propylthiouracil for nearly a year, but during the second course adequate dosage was given and the hyperthyroidism was well controlled. Concurrently she received cyclic progesterone therapy to regulate the cycle, and she finally entered a phase of three months' amenorrhea which may have been a pregnancy ending in abortion. One month later she conceived and was delivered in nine months of the first of her 2 normal children.

These observations suggest that during hyperthyroidism, and perhaps even before the hyperthyroidism is recognizable, there is an increased incidence of disturbed ovarian function. They further suggest that control of the hyperthyroidism has a favorable effect upon the reproductive cycle.

Of the 31 pregnancies studied, including 3 which have not reached term, 6 had been completed before the patients first presented themselves for treatment. Three of these infants were apparently normal in every way, 1 (No. 18) was two months premature and did not survive, 1 (No. 13) was born with spina bifida and died shortly after birth, and a third was born at term and died during the neonatal period from an unknown cause. By contrast, the 22 pregnancies which were completed during or following treatment yielded 22 living children.

Influence of pregnancy on hyperthyroidism

The older view that pregnancy is to be regarded as a grave complication of hyperthyroidism and one which might aggravate the disease and even lead to thyrotoxic crisis was not supported by this study. More recent observers, too, have come to look upon hyperthyroidism during pregnancy with no great concern. Mussey (16) concluded that pregnancy makes hyperthyroidism no better and no worse and Javert (5) observed that thyrotoxicosis is ameliorated by pregnancy. Engstrom *et al.* (14) found that pregnancy decreased the required dosage when treatment was carried out with iodine plus an antithyroid drug. The observations reported here suggest that pregnancy exerted a beneficial effect upon the hyperthyroidism. Not only was the disease easily controlled by the usual doses of the antithyroid drugs, but the incidence of lasting remission was high. Thus, of the 18 patients who completed at least one course of antithyroid therapy and had undergone at least one pregnancy, 15 continued in good health after treatment was discontinued. The lengths of these remissions, shown in Table 4, exceeded two years in 13 instances.

The 3 patients who did not achieve a remission are of interest. In each, the hyperthyroidism was of long standing and in 2 it had previously been treated by subtotal thyroidectomy. Patient No. 4 was treated by subtotal thyroidectomy in 1942 at the age of 21 and with iodine thereafter until propylthiouracil was started in 1946. After fifteen months of antithyroid therapy, during the last eight of which she was pregnant, she seemed to be well but continued to have atypical symptoms and three years later treatment was resumed. The rapid subsidence of the symptoms indicated the likelihood of continued mild hyperthyroidism after therapy and during the second pregnancy. Patient No. 5 had had 4 normal children and 1

TABLE 4. THE LENGTHS OF REMISSION OF THE THYROTOXICOSIS AFTER ANTITHYROID THERAPY WAS DISCONTINUED

	No. of patients
Less than 2 years	2
2–3 years	6
3–4 years	5
More than 5 years	2
	15
Relapse	3

miscarriage. The hyperthyroidism probably dated from the time of the miscarrage in 1943, when the patient was 32 years old, and with certainty not later than 1945. Subtotal thyroidectomy in 1947 had practically no effect on the hyperthyroidism, which thereafter was partly controlled by iodine and later by propylthiouracil. The former of 2 pregnancies during propylthiouracil treatment (her fifth) was normal but thereafter the hyperthyroidism was poorly controlled by inadequate and intermittent treatment and when first seen when five months pregnant, the hyperthyroidism was severe. There had been a most extensive regeneration of thyroid remnants and the whole anterior aspect of the neck was occupied by large confluent masses which extended from the mandible to below the sternum. The hyperthyroidism was controlled in one month with 5 milligrams of methylmercaptoimidazole every six hours and a month later she had a difficult premature delivery as noted above. Six months later therapy with radioiodine was undertaken because of the unsightly goiter. A first dose of 21 millicuries brought about partial improvement of the hyperthyroidism and a marked reduction in the size of the thyroid masses but a second dose of 8 millicuries was required five months later to effect a

nearly complete disappearance of the enlargements and to restore euthyroidism. The third patient who did not achieve a remission (No. 6) had received a single, eight-month course of propylthiouracil therapy in 1946 and treatment had to be resumed in 1951. She, too, like Patient 4 previously cited, may in retrospect have been mildly thryotoxic after therapy and during her second pregnancy.

DISCUSSION

These observations suggest that antithyroid therapy can safely be continued throughout pregnancy without harm to either the mother or child. They suggest further that gestation is more apt to be normal when the hyperthyroidism is thus adequately treated than when it is not. The findings also indicate that, if congenital anomalies occur during pregnancy complicated by hyperthyroidism, these anomalies are not brought about by the treatment.

When antithyroid drugs are used during pregnancy a full therapeutic dose can be employed in order to restore metabolic equilibrium as quickly as possible. It is clear, however, that hypothyroidism should not be induced and therefore the dosage should be reduced as soon as euthyroidism is achieved. Excessive dosage and consequent hypothyroidism might increase the risk of abortion in early pregnancy and could, in late pregnancy, cause hypothyroidism and goiter in the fetus. During pregnancy, especially during the last trimester, it may be difficult to evaluate the status of thyroid function. The increased rate of heat production, the flushed, warm, moist and pigmented skin, the tachycardia, easy fatigue, and breathlessness might suggest hyperthyroidism in the normal pregnant woman as term approaches. Contrariwise a false impression of early myxedema might be suggested by those patients who exhibit excessive weight gain, edema, puffiness of the face, pallor, lethargy, and somnolence. For these reasons it is probably advisable to administer a small dose of antithyroid drug, such as 50 milligrams of propylthiouracil every twelve or eight hours, during the last three months of pregnancy. Though this was the course usually followed in this investigation, an alternative and perhaps better procedure involves the use of full doses of the antithyroid agent counterbalanced with a full supplement of thyroid. The larger dose of antithyroid drug would insure against significant thyrotoxicosis, while 2 to 4 grains of thyroid daily would be adequate to prevent hypothyroidism. This procedure has often been employed in other cases in which, for one reason or another, it was not feasible to observe the patients frequently to adjust the dosage of antithyroid drug.

In the present study the medication was usually discontinued at the time of delivery. This permitted the baby to be nursed without danger of

transmission of antithyroid drug to the infant in the milk. If continued therapy should be required, the child should be fed artificially.

SUMMARY

A study of hyperthyroidism in association with pregnancy supported the view that in hyperthyroidism there is an increased incidence of menstrual irregularity, diminished fertility, and a higher than normal rate of fetal loss through miscarriage and stillbirth. Nineteen patients suffering from hyperthyroidism were treated with antithyroid drugs during or shortly before pregnancy. The 22 completed pregnancies yielded 22 living children who showed no evidence of thyroid disturbance or goiter. There were 3 premature deliveries. Sixteen of the mothers remained well after the antithyroid therapy was stopped, whereas 3 required further treatment. It was concluded that pregnancy is beneficial to hyperthyroidism and that antithyroid therapy alone is an effective form of treatment.

Acknowledgment

This study was made possible by the generous cooperation of the private physicians who referred these patients for treatment. For assistance in carrying out the investigation I am indebted to my associates and especially to Drs. W. P. VanderLaan, M. M. Stanley, and M. S. Raben.

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1-METHYL-2-MERCAPTOIMIDAZOLE: A NEW ACTIVE ANTITHYROID AGENT*

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SINCE thiouracil, the first antithyroid drug, became available, additional related compounds have received clinical trial. Chief among the group (Table 1) are thiourea, thiobarbital, aminothiouracil, propylthiouracil, methylthiouracil, iodothiouracil, Meprocil (a combination of methylthiouracil and propylthiouracil) and the newest member, 1-methyl-2-mercaptoimidazole (Tapazole).[1] As each new antithyroid drug becomes available it not only promptly receives clinical trial to determine its antithyroid effectiveness and dosage but, more important, the incidence of

TABLE 1. ANTITHYROID DRUGS

	Dosage (mg.)	Incidence of reactions (per cent)
Thiouracil	600	10
Thiourea	200–300	16
Thiobarbital	50	28
Aminothiouracil	—	*
Propylthiouracil	200–400	1.6
Methylthiouracil	200–300	13
Iodothiouracil	200–300	*
Meprocil (methylthiouracil and propylthiouracil)	200–300	*
Tapazole (1-methyl-2-mercaptoimidazole)	20–30	6

* Too few treated to indicate true incidence of reactions.

toxicity, since there is a constant effort to find a drug which can be safely administered. When propylthiouracil became available and the incidence of reactions was found to be only 1.6 per cent, the use of thiouracil and thiobarbital was abandoned because of their higher reaction rates. Simi-

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[1] Obtained from Dr. D. C. Hines, Eli Lilly & Co., Indianapolis, Indiana.

larly, methylthiouracil is not routinely used because it has a reaction incidence of 13 per cent.

Clinical experience is now being gained with the newest antithyroid drug, 1-methyl-2-mercaptoimidazole (Tapazole). This substance was investigated by Stanley and Astwood (1) and found to have pronounced antithyroid activity. In testing this drug by comparing its inhibitory effect on radioactive iodine uptake with that of thiouracil, it was found to be 100 times as effective as thiouracil. These workers reported that preliminary studies on 30 patients with hyperthyroidism treated with this compound confirmed this high degree of effectiveness.

The first published report on the clinical use of 1-methyl-2-mercaptoimidazole was by Reveno and Rosenbaum (2) who treated 18 hyperthyroid patients and found that the potency of the drug is approximately 25 times that of thiouracil. They observed no toxic effect in doses of 4 to 10 mg. per day. Beierwaltes (3) treated 9 hyperthyroid patients with a daily dose of 6 to 40 mg. for an average period of two months and observed a satisfactory fall in the basal metabolic rate in all cases. No toxic reactions were observed. It was his opinion that 1-methyl-2-mercaptoimidazole is approximately 7 times as effective as propylthiouracil.

Hines (4) of Eli Lilly and Company (who supply the drug under the name of Tapazole) reported that approximately 1,100 patients have been treated to date, with a reaction incidence of 4.8 per cent, most of the reactions involving the skin—rash and urticaria. It is Hines' opinion that Tapazole is more effective and acts more quickly than any of the thiourea derivatives.

This report deals with a review of our observations on the first 100 of 180 hyperthyroid patients who were given Tapazole. These first 100 patients included 82 who had primary hyperthyroidism (9 of these having recurrent disease) and 18 patients who had hyperthyroidism due to an adenomatous goiter. Of these 100 patients, 93 received Tapazole in preparation for a subtotal thyroidectomy and 7 patients received it as maintenance medical treatment. The range of age was wide, from 10 to 75 years, and the sex distribution was as usual in hyperthyroidism, with 85 per cent of the patients being women.

DOSAGE

The suggested initial daily dose of Tapazole was 6 to 15 mg. This dose was soon found to be inadequate to bring about a response comparative to that obtained from the standard daily dose of 200 to 400 mg. of propylthiouracil. The dose was gradually increased to 20 to 40 mg. daily, which amount seems to have an effect equivalent to that of 200 to 400 mg. of propylthiouracil, indicating that Tapazole is 10 times as active as propyl-

thiouracil. It is thought, therefore, that the daily dose of 4 to 10 mg. reported by Reveno and Rosenbaum is below the active therapeutic level. The daily dose of Tapazole which we finally adopted was 20 mg. for patients with primary hyperthyroidism whose goiters were small to moderate in size, and 30 mg. for patients with large goiters. Patients with adenomatous goiters received 30 mg. daily and if the goiter was extremely large, a dose of 40 mg. or even 50 mg. daily. This plan of treating patients with Tapazole resulted in a fall in the metabolic rate of approximately one point per day for previously untreated primary hyperthyroidism and half a point per day for adenomatous goiter. This decline in the basal metabolic rate compares with the fall observed when a dose of 200 to 400 mg. of propylthiouracil is given daily.

DURATION OF TREATMENT

The patients receiving Tapazole in preparation for thyroidectomy took the medication for periods ranging from ten days to six months. Approximately 60 per cent were treated for forty to seventy days; 25 per cent, for less than forty days; and 15 per cent, most of whom were patients with adenomatous goiters, for more than seventy days.

The 7 patients being maintained with Tapazole have taken it for periods of ten to seventeen months. Five of these 7 patients are on maintenance treatment because of complicating disease making thyroidectomy inadvisable; 1 patient has severe chronic ulcerative colitis, 2 have serious hypertensive vascular disease, 1 has serious hepatic disease (cirrhosis) and 1 has progressive amyotrophic lateral sclerosis. The 2 other patients who are on maintenance treatment have recurrent primary hyperthyroidism. All of these patients are euthyroid and are being maintained on 2.5 to 5 mg. of Tapazole per day.

REACTIONS

There were 6 reactions to Tapazole among the 100 patients or an incidence of 6 per cent (Fig. 1). All of these were skin reactions and in 3 patients (Fig. 1, Cases 1, 2 and 3) they were sufficiently troublesome to necessitate withdrawal of treatment. In 2 of these latter patients (Cases 1 and 2) there was a generalized urticarial rash and in 1 (Case 3) there was troublesome stomatitis. In Case 3 the patient had previously been intolerant to propylthiouracil. These 3 patients were give further antithyroid treatment. In Case 1 propylthiouracil was tolerated but in Cases 2 and 3 there was sensitivity to thiouracil.

Three (Fig. 1, Cases 4, 5 and 6) of the 6 patients who had skin manifestations were able to continue treatment with Tapazole. In Case 4 the dose of Tapazole was reduced from 50 to 30 mg. and Pyribenzamine was given

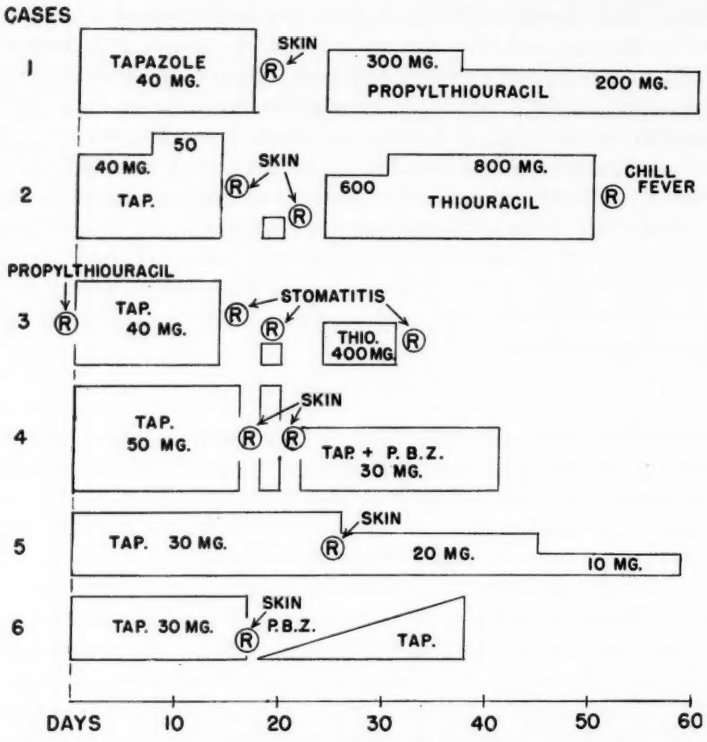

FIG. 1. Reactions to Tapazole in 6 patients with hyperthyroidism. The dose administered, time of onset of reaction and type of reaction are shown. The methods used for further treatment of the hyperthyroidism are also indicated.

without further skin reaction. By reducing the dose of Tapazole to 20 mg. and later to 10 mg., it was possible to continue treatment in Case 5. Case 6 was managed by giving Pyribenzamine to relieve the pruritic skin eruption; then Tapazole was started in 5-mg. doses and slowly increased to a 30-mg. dose, without a return of the skin eruption.

The 6 reactions began on the fourteenth day in 2 patients, on the seventeenth day in 3, and on the twenty-sixth day in 1 patient.

Six of the group of 100 patients had previously been found to be sensitive to propylthiouracil (Fig. 2). All had skin reactions and 2 also showed some degree of granulocytopenia. These 6 patients tolerated long periods of treatment with Tapazole.

All of the patients treated with Tapazole were ambulatory and they returned every two to three weeks for re-examination, including white and differential blood counts. In no instance was there observed evidence of

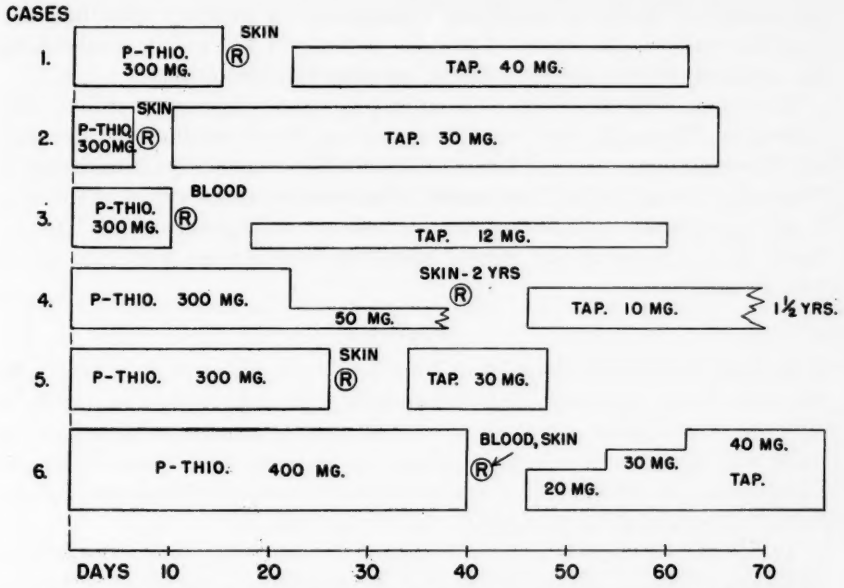

FIG. 2. Reactions to propylthiouracil in 6 patients with hyperthyroidism who subsequently tolerated prolonged administration of Tapazole.

white blood cell depression. It is, however, to be expected that since other agents of the antithyroid group do cause white blood cell depression, in due time such a case will be observed.[2]

There is some evidence to suggest that there is a definite relationship between the size of the dose of Tapazole and the development of a reaction, since 4 of the 6 patients (Fig. 1) received daily doses of 40 to 50 mg. Since it has been established that a daily dose of 30 to 40 mg. results in a satisfactory lowering of the basal metabolic rate, there seems little indication for larger doses, especially if it can be proved that larger doses lead to a higher rate of reactions.

Myxedema was observed to occur in 2 patients with primary hyperthyroidism. One patient had received 50 mg. of Tapazole daily for one month and the other had received 30 mg. daily for 140 days. As in our past experience with the antithyroid drugs, in no patient with hyperthyroidism due to adenomatous goiter was myxedema observed even after prolonged treatment with Tapazole in large doses (40 to 50 mg.). It is, therefore, of clinical advantage to obtain serial determinations of blood cholesterol as

[2] Since analyzing these first 100 cases we have observed 1 case in which rather severe granulocytopenia (15 per cent) developed while the patient was taking Tapazole.

an additional guide to antithyroid treatment in patients with primary hyperthyroidism. An elevated plasma cholesterol will aid in establishing the presence of myxedema before it becomes symptomatic.

The thyroid glands of the patients with primary hyperthyroidism who were given Tapazole were found, at operation, to be satisfactorily involuted. These patients received Lugol's solution (10 drops daily) in addition to Tapazole during the last three weeks of preoperative therapy, according to a plan previously established for the use of antithyroid drugs. The patients with adenomatous goiters and hyperthyroidism were not given Lugol's solution.

SUMMARY

Tapazole (1-methyl-2-mercaptoimidazole), a new antithyroid drug, was found to be an effective antithyroid agent. Clinically it was found to be 10 times (or slightly more) as active as propylthiouracil. The suggested daily dose of Tapazole is 20 to 30 mg. for patients with primary hyperthyroidism and 30 to 40 mg. for patients with adenomatous goiters, the size of the goiter determining the size of the dose.

There were 6 reactions from Tapazole in the 100 patients receiving treatment, an incidence of 6 per cent. In 3 patients treatment had to be withdrawn but in 3 patients further treatment with Tapazole was possible by altering the dose or by adding an antihistaminic drug.

This experience with Tapazole indicates that it is an active antithyroid substance. The incidence of reactions is higher than with propylthiouracil (6 per cent as compared with 1.6 per cent), but none of the reactions was serious and agranulocytosis was not observed in the initial group of 100 patients studied. Since completion of this study, however, 1 case was observed in which severe granulocytopenia (15 per cent) developed, indicating that this antithyroid drug also has toxic potentialities.

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COLUMN CHROMATOGRAPHY OF THYROID GLAND HYDROLYSATES*

Van Meter Prize Award Essay

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THE constitution of proteins containing iodine has been the subject of study since Baumann's discovery of the occurrence of iodine in the thyroid gland. The investigations of Kendall (1) and of Harington (2) established, by classic chemical methods of isolation and characterization, the presence of thyroxine and diiodotyrosine in thyroid gland protein; and Ludwig and von Mutzenbecher (3) recovered these amino acids and also monoiodotyrosine from iodinated casein. Pitt-Rivers (4) has recently analyzed critically the methods for the identification and measurement of the iodinated components of natural and artificial thyroproteins.

The past decade has witnessed the development of chromatographic methods as powerful analytic tools and their application as aids in the separation and identification of the components of a variety of biologic systems (5). In the field of thyroid biochemistry the use of partition chromatography on paper in conjunction with radioactive iodine as an indicator (6) has been particularly fruitful. The studies of Fink and Fink (7) of paper chromatograms of hydrolysates prepared from the thyroid glands of rats previously injected with radioactive iodine indicated the presence of a substance indistinguishable from monoiodotyrosine. This observation was subsequently confirmed (8, 9) and extended by Taurog and his associates (9, 10) who showed that monoiodotyrosine is a metabolic precursor of diiodotyrosine, and not merely a breakdown product formed during hydrolysis. The technique of paper chromatography has also been successful in characterizing the iodine in urine (11), in demonstrating the occurrence in the thyroid gland of free thyroxine (12) and of monoiodotyrosine and diiodotyrosine (8), and by application to studies

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of the plasma iodine of animals (12, 13, 14) and of man (15), has lent further support to the concept that the circulating thyroid hormone is thyroxine (16).

The present work is a study of the use of chromatographic columns of starch and of cellulose in the separation of iodine-containing amino acids as applied to the labelled compounds formed in the thyroid gland of the rat following the administration of radioactive iodine (I^{131}).

EXPERIMENTAL

1. *Preparation of the sample.* Male Sprague-Dawley rats (100–200 grams), which had been maintained for several weeks on a low-iodine diet (280 micrograms of iodine per kilogram of food), were injected intraperitoneally with 30 to 60 microcuries of carrier-free I^{131}. At intervals after injection varying between one and one hundred and twenty hours the animals were killed by exposure to chloroform, the thyroids were removed, and each gland was placed in a centrifuge tube containing 1 cc. of 2 N NaOH. An air condenser was attached to prevent evaporation, and hydrolysis was carried out on the steam bath for fifteen to eighteen hours. The hydrolysate was then brought to pH 3 by the addition of 4 N HCl and the solution was extracted three times with 3-cc. portions of *n*-butanol saturated with water, the butanol layer being removed each time by means of a fine-tipped rubber-bulb pipette. The combined butanol extracts, containing 90 to 95 per cent of the I^{131} present in the alkaline hydrolysate, were transferred to a 250-cc. flask, evaporated to dryness under reduced pressure, and the residue taken up with three successive 0.5-cc. portions of the appropriate solvent; for extracts subsequently to be fractionated on starch columns the solvent used was *n*-butanol 10: benzyl alcohol 10: 1 N HCl 0.25, whereas for cellulose columns the composition was *n*-butanol 7.5:acetic acid 2.0:water 0.5. In order to keep the volumes of the samples conveniently small, a quantitative removal of the residue from the flask was not attempted; however, the washing procedure described removed better than 90 per cent of the radioactivity. The solution was then centrifuged to remove insoluble material carried over from the flask in the course of transfer of the liquid, and a portion (0.4 to 0.6 cc.) of the clear solution was placed on the column. In many experiments, 0.08 to 0.12 cc. of a solution containing, in the appropriate solvent, approximately 1 to 2 micromoles each of thyroxine, diiodotyrosine, and monoiodotyrosine was added to the sample just before placing the latter on the column.[1] A small aliquot of the sample loaded on the column was used for the determination of radioactivity.

In some experiments, the butanol extract of the acidified hydrolysate was extracted with Blau's reagent (18) for the separation of the thyroxine fraction, and aqueous and organic layers were washed with butanol and alkali, respectively. The aqueous phase was then acidified to pH 3 and extracted with butanol. Both butanol extracts were then concentrated and chromatographed on starch columns.

2. *Preparation and operation of columns.* Starch columns 28 to 30 cm. tall and 0.9 cm. in diameter were prepared from Aroostocrat potato starch according to the methods of Stein and Moore (19), using glass chromatograph tubes provided with a sintered glass base. The composition of the solvent was *n*-butanol 100:benzyl alcohol 100:water

[1] Solution of the crystalline thyroxine (Roche-Organon), diiodotyrosine (Hoffmann-LaRoche) and monoiodotyrosine (prepared according to the method of Harington and Pitt-Rivers (17) was facilitated by adding a small drop of 4 N HCl per cc. of solution.

26; the water content of the solvent was less than that used by Moore and Stein for amino acid separation in order to prevent phase separation with change in room temperature. Thiodiglycol (0.5 per cent) was incorporated into the solvent in some instances. Columns were pretreated with 8-hydroxyquinoline and operated under a pressure of 10 to 12 cm. of mercury to provide a flow rate of 0.8 to 1.2 cc. per hour. Slower flow rates (0.2 to 0.4 cc. per hour) did not provide better resolution. Collection of the effluent was begun directly after the sample had been added to the column, without collecting a forefraction.

Cellulose columns were made by a modification of the method of Peterson and Reineke (20) in glass tubes 60 cm. tall and 0.95 cm. in diameter; the lower end of the tube was lightly tapered, a plug of glass wool in the constricted region serving as a support for the cellulose. Twelve grams of powdered cellulose (Solka-Floc BW 200) taken from a batch which had previously been washed on a Büchner funnel successively with water, 2 N HCl, water, acetone, and ether and then air dried, was slurried in 75 cc. of solvent (butanol 75:glacial acetic acid 10:water 15) and poured into the tube, using a glass extension tube. The column was packed by compressed air at a pressure of 60 cm. of mercury; when packing was complete the height of the column was 50 cm. The column was then equilibrated with the solvent by allowing 75 to 100 cc. to flow through the column under a pressure head of 3 to 5 cm. of solvent above the column. The liquid above the column was then withdrawn, the cellulose surface tamped lightly with the flattened end of a glass rod, and 100 mg. of 8-hydroxyquinoline dissolved in 2 cc. of solvent was added, with washing, to the column. After 100 cc. of solvent had passed through the column and the increasingly darkening green band had emerged, the sample to be fractionated was applied to the column, allowed to run in under gravity, and the sides of the tube rinsed twice with 0.5-cc. portions of solvent. At this point a two-inch length of rubber tubing equipped with a glass delivery tube and a screw-clamp was attached to the lower end of the column, and the flow rate was thereby adjusted to 0.8–1.0 cc./hour. Faster flow rates generally resulted in inferior resolution. The effluent was allowed to drip into a graduated cylinder until a forefraction of 20 cc. (nearly one column volume) had been collected.

The columns were mounted on an automatic fraction collector operating on a constant time interval basis. The fractions were collected in uniform, flat-bottomed glass vials 125×15 mm., the volume of the fractions generally ranging from 0.25 to 0.5 cc. The volume of each effluent fraction was determined from the average obtained by direct measurement of a number of fractions.

3. *Measurements of* I^{131}. Measurements of radioactivity were made by gamma-ray counting of liquid samples, using a Sylvania Geiger-Müller tube (GG 306) in the apparatus described by Raben (21). For determining the I^{131} of the effluent fractions, the flat-bottomed collection tubes containing them were placed directly on the surface of the tube through a hole in the lead shielding, of diameter slightly greater than the tube. The characteristics of the system were such that 1 microcurie of I^{131} in a volume of 1 cc. produced 255 counts/sec. Variations of the count with change in volume were allowed for by correcting all counts to a standard 1-cc. volume, by reference to a calibration table. The latter was constructed from counts observed at different volumes when 0.1-cc. increments of solvent were successively added to a standard sample of I^{131} in 0.2-cc. volume. The amount and location of radioactivity remaining in the column after emergence of the major effluent bands were determined by marking the chromatograph tube in 2-cm. sections and measuring the radioactivity in each section as it was held horizontally over the orifice in the counting tube shield.

4. *Other procedures.* After the measurement of the I^{131} in the effluent fractions had been completed, photometric determination of ninhydrin-reacting material (22) was performed on aliquots from each tube in those experiments in which amino acid carriers had been added to the sample prior to chromatography. The quantities of thyroxine, diiodotyrosine, and monoiodotyrosine in the samples chromatographed were too small, in the absence of added carriers, to be detectable by the procedure employed. One-dimensional ascending paper chromatograms were made of selected effluent fractions and of the original sample, using a solvent of the same composition as that used on the cellulose columns. Radioautographs of the developed chromatograms were prepared by allowing them to remain in contact with "no-screen" x-ray film for periods of two to six days. Details of the methods used for paper chromatography and radioautography have been previously described (15).

RESULTS

Analysis of the curves obtained on plotting the concentration of I^{131} in the effluent fractions against the volume of effluent from both starch

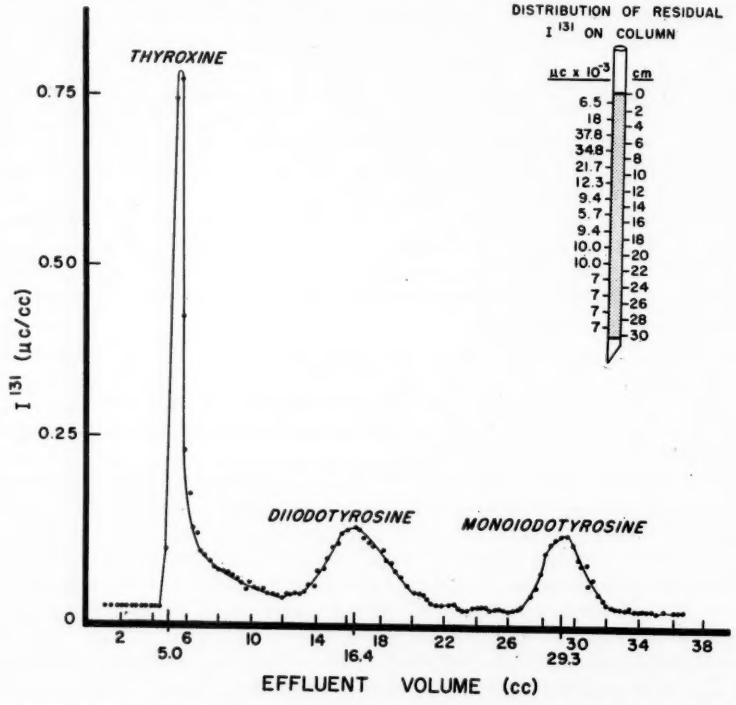

FIG. 1. Starch column separation of labelled constituents of the thyroid gland of a rat twenty-three hours after the administration of I^{131}. Column 30 cm. tall ×0.9 cm. diameter. Solvent: *n*-butanol 100:benzyl alcohol 100:water 26. Flow rate 0.84 cc./hour. The chromatographed sample (no added carrier) contained 2.24 μc. I^{131}; 1.94 μc. emerged between 4.5 and 34 cc. Distribution of I^{131} remaining in the column (0.211 μc.) after the emergence of the monoiodotyrosine band is indicated in the insert.

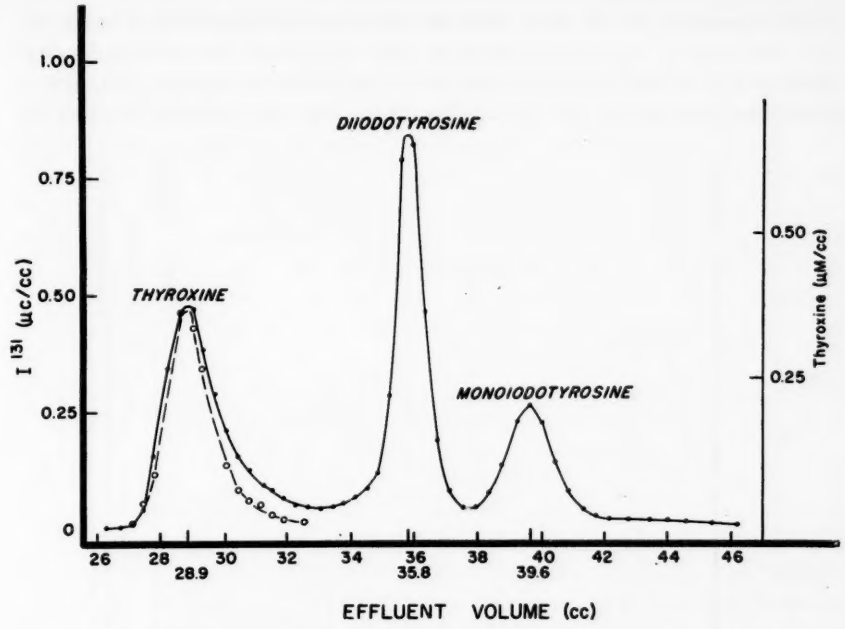

FIG. 2. Cellulose column chromatogram of the labelled components in the thyroid of a rat twenty-four hours after injection of I^{131}. Column 54 cm. tall and 0.95 cm. in diameter. Solvent: *n*-butanol 75:acetic acid 10:water 15. Flow rate 0.8 cc./hour. The sample, 3.0 μc., was placed on the column with added thyroxine carrier; 2.79 μc. emerged in the effluent between 27 and 43 cc. Solid circles, unbroken line, represent I^{131} concentration; open circles, broken line represent the concentration of thyroxine determined photometrically.

and cellulose columns indicated the occurrence of three distinct components, corresponding to thyroxine, diiodotyrosine, and and monoiodotyrosine, the order of emergence being the same in both types of columns (Figs. 1 and 2). Preliminary experiments in which the pure amino acids singly and in combination had been added to starch columns of the dimensions used, had shown that the peak of the effluent bands varied little from one experiment to another; thyroxine emerged at 5 cc. (the moving solvent front), diiodotyrosine at 16 cc., and monoiodotyrosine at 31 cc. Characterization of the effluent radioactive bands from starch columns of thyroid hydrolysate was facilitated by adding carrier thyroxine, diiodotyrosine, and monoiodotyrosine to the sample to be chromatographed, and observing the correspondence between radioactivity and carrier (ninhydrin equivalent) in the effluent fraction (Fig. 3). The correspondence between carrier and I^{131} for diiodotyrosine and monoiodotyrosine was good, the ratio of the graphic representation of concentration

of carrier and of I^{131} at each point of these curves approaching unity. It was consistently observed, however, that although I^{131} and ninhydrin values of the ascending limb of the first emergent peak agreed well, divergence was marked on the descending limb, the radioactivity tending to

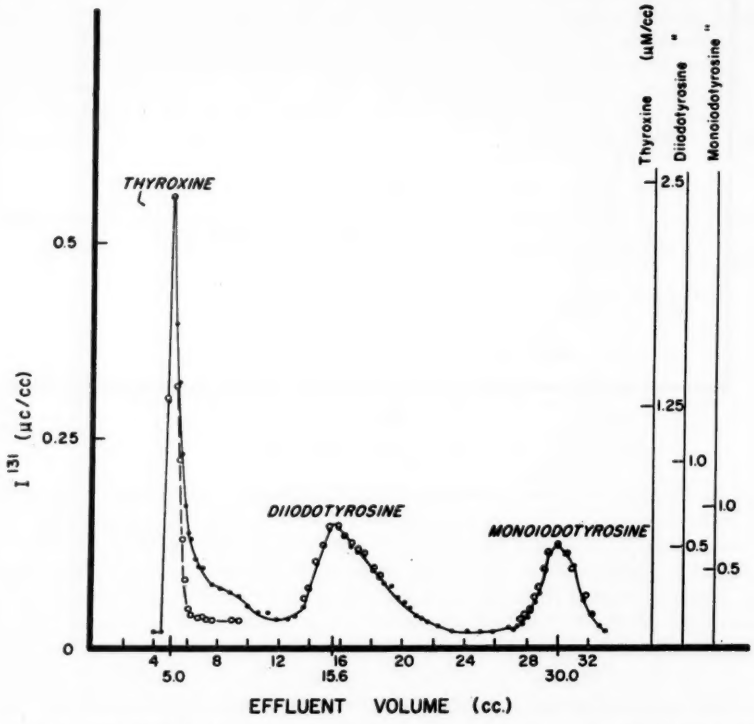

FIG. 3. Starch column chromatogram of rat thyroid hydrolysate. The thyroid gland was removed eight hours after the administration of I^{131}. Carrier thyroxine, diiodotyrosine, and monoiodotyrosine were added to the sample prior to chromatography. Column 30 cm. $\times$0.9 cm. Solvent: *n*-butanol 100:benzyl alcohol 100:water 26:thiodiglycol 1.0. Flow rate 0.4 cc./hour. The sample placed on the column contained 2.22 μc.; 1.90 μc. emerged in the three bands indicated. I^{131} concentration is represented by solid circles, unbroken line; and carrier amino acid concentration (ninhydrin reaction) by open circles, broken line.

tail out and slope down into the beginning of the diiodotyrosine curve, while the colorimetrically determinated thyroxine curve returned to the base line more rapidly and symmetrically. The iodinated amino acids on starch emerged ahead of any other ninhydrin-reacting substances in the butanol extract; phenylalanine, however, emerged close behind monoiodo-

tyrosine and occasionally the descending limb of the curve of added monoiodotyrosine was distorted by phenylalanine.

Identification of the emergent radioactive bands from cellulose columns was aided by paper chromatography of material from each band. Ten to

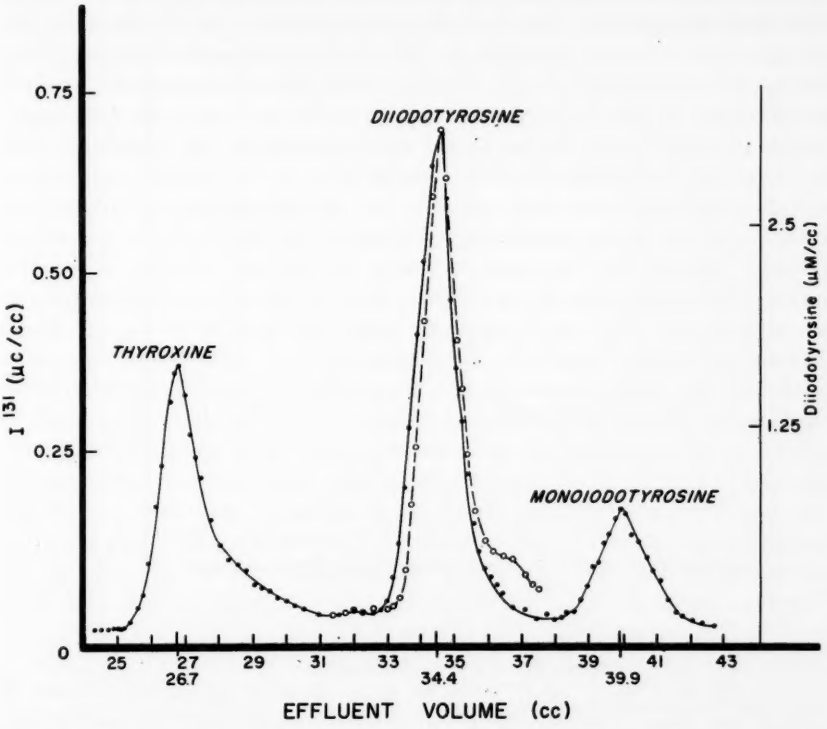

FIG. 4. Cellulose column chromatogram of labelled thyroid components twenty-seven hours after the rat received I^{131}. Column dimensions and developing solvent composition were as described in Figure 2. Flow rate 0.25–0.4 cc./hour. Diiodotyrosine carrier was added to the sample prior to chromatography. Solid circles, unbroken line, represent I^{131} concentration; and open circles, broken line, the photometrically determined concentration of diiodotyrosine. Ninhydrin-reacting material present in the sample caused the deviation of the lower portion of the descending limb of the photometric diiodotyrosine curve.

15 cu. mm. of solution from a tube near the apex of each peak was spotted on a paper, carriers applied to the same spot, the chromatogram developed and a radioautograph prepared from it. Comparison of the position of the radioactivity as indicated by the radioautograph with the position of the corresponding iodinated amino acid on the paper as revealed by color

development after spraying with ninhydrin and heating, showed that the first effluent band corresponded to thyroxine, the second to diiodotyrosine, and the third to monoiodotyrosine. Radioautographs indicated, in addition to the single major dark spot corresponding to the amino acid, fainter areas at positions corresponding to those of iodine and iodide ($R_f = 0.95$ and 0.12 respectively). This has been interpreted to be the result of decomposition occurring during paper chromatography rather than to grossly incomplete resolution on the column, since the chromatogram of each band seldom revealed significant contamination with the other two amino acids. Decomposition during paper chromatography has been described by several investigators (10, 23). Identification of the effluent bands from cellulose columns was also possible by adding carrier thyroxine and diiodotyrosine to the sample and proceeding as described for the starch column, but only in instances in which the specific activity of the I^{131}-containing compounds was sufficiently high to permit chromatography of an aliquot representing a relatively small fraction of the entire gland hydrolysate (Figs. 2 and 4). Thyroxine emerged well before any other ninhydrin-reacting component of the sample, but the close emergence of diiodotyrosine and phenylalanine would distort the descending limb of the curve of the former, if the latter were present in comparatively large quantity (Fig. 4). In contrast to the relative constancy of the values for the emergent active peaks from starch columns, was the considerable variation noted in these values with cellulose columns, although the order of emergence was unchanged. On four separate runs on one column, for example, the peak of the diiodotyrosine band occurred at 38.7, 41.2, 34.5, and 35.7 cc. respectively. One of the factors which may have been concerned in this variability was the change in behavior of the solvent (butanol-acetic acid) with time because of ester formation, since R_f values on paper, especially of monoiodotyrosine and diiodotyrosine, become smaller in solvent more than one week old (15).

The column chromatograms prepared from thyroid hydrolysates indicated that the organic iodine was largely accounted for by the three amino acids, thyroxine, diiodotyrosine, and monoiodotyrosine, as found by Taurog and his colleagues (10). Inorganic iodide was not found, presumably because a step in the preparation of the sample included evaporation to dryness of an acid butanol extract. In chromatograms prepared from animals killed within one hour after I^{131} administration, the monoiodotyrosine and diiodotyrosine bands accounted for most of the radioactivity, the thyroxine band being small. At later intervals (72 to 120 hours after injection) relatively much more of the total I^{131} was in the thyroxine band, and the monoiodotyrosine I^{131} contributed less to the total (Fig. 5). Thus, the chromatogram prepared from a gland removed fifty minutes after the

animal had received I^{131} indicated that 18 per cent of the organic I^{131} was present as thyroxine, 57 per cent as diiodotyrosine, and 25 per cent as monoiodotyrosine; whereas, in the thyroid of a rat killed 120 hours after the administration of I^{131}, 45 per cent was present as thyroxine, 40 per cent as diiodotyrosine, and 15 per cent as monoiodotyrosine. At intermediate intervals, 35 to 45 per cent of the I^{131} in the chromatographed samples

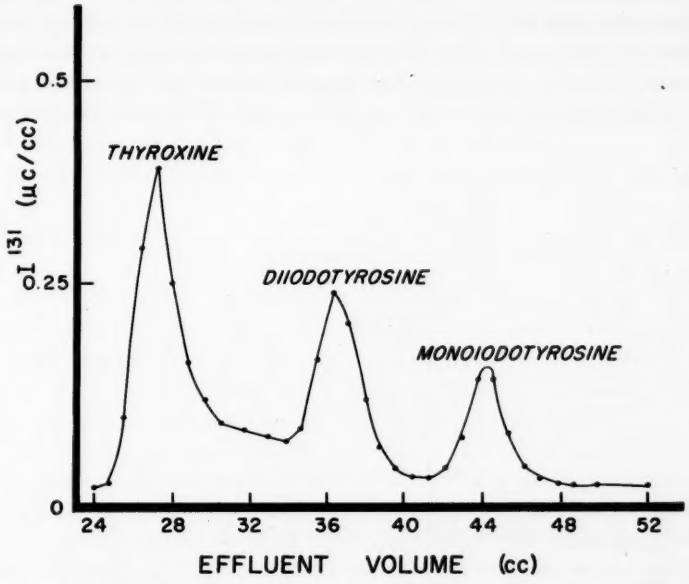

FIG. 5. Cellulose column chromatogram of labelled thyroid constituents. The thyroid was removed forty-five hours after the administration of I^{131} to the rat. Column dimensions and solvent composition were as described in Figures 2 and 4. Flow rate 2.4 cc./hour. The sample contained 2.86 μc.; 3.04 μc. emerged in the indicated effluent. No carriers were added.

existed as thyroxine, 40 to 45 per cent as diiodotyrosine, and 15 to 20 per cent as monoiodotyrosine. The relative symmetry of the effluent curves from cellulose columns was suggestive of their homogeneity, the absence of marked distortion of the curves and of peaks of activity other than the three mentioned being evidence for the absence in quantity of other labelled organic iodine compounds. Paper chromatographic studies by several investigators have indicated the presence of a number of unidentified iodine-containing components in the thyroid (6, 8, 12). The existence of small quantities of compounds with distribution characteristics between those of thyroxine and diiodotyrosine has not been excluded in

the present work because of the tailing of the first effluent band, particularly on starch columns. Many factors, however, may cause asymmetry even of homogeneous materials emerging from a column (24); and the inability to detect by paper chromatography of effluent fractions from the tailing zones, discrete spots distinct from thyroxine and diiodotyrosine, would make the significance of these zones uncertain. Chromatograms on starch of the I^{131} fractions of the butanol extract, which were respectively, nonextractable and extractable by Blau's reagent, indicated the former to be thyroxine without detectable admixture of monoiodotyrosine and diiodotyrosine, whereas the latter was largely mono- and diiodotyrosine but with a small quantity of I^{131} (about 10 per cent of the total) corresponding

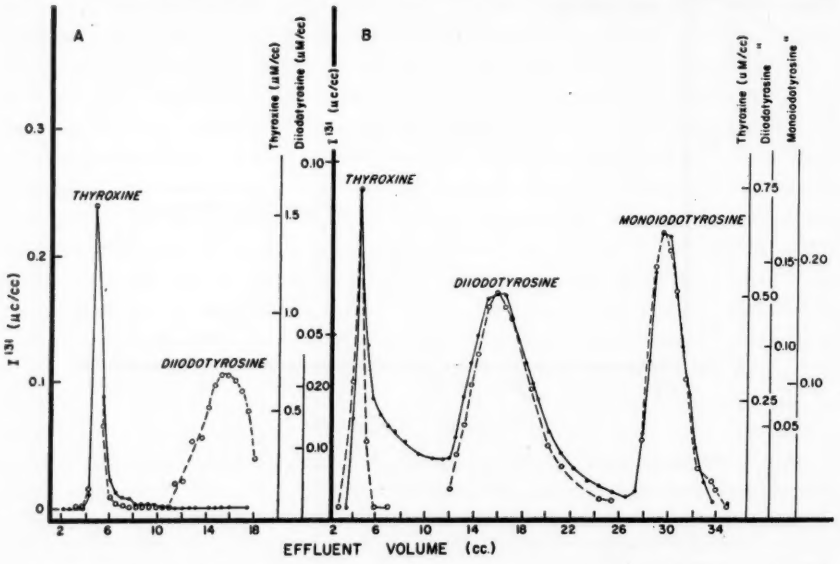

FIG. 6. Starch column chromatograms of thyroid hydrolysate. The original acid-butanol extract was shaken with Blau's reagent, and the fractions extractable and non-extractable by alkali were chromatographed separately. Column 27 cm. $\times$ 0.9 cm. Solvent: *n*-butanol 100: benzyl alcohol 100: water 26: thiodiglycol 0.5. Flow rate 1.10 cc./hour. Carrier thyroxine, diiodotyrosine, and monoiodotyrosine were added. Solid circles, unbroken line, represent I^{131} concentration; and open circles, broken line, represent carrier amino acid concentration.

A. "Thyroxine" fraction (butanol extractable and not re-extractable in NaOH). The sample contained 0.298 μc.; 0.248 μc. was recovered in the effluent between 4.5 and 15 cc. No radioactive diiodotyrosine was detectable.

B. "Diiodotyrosine" fraction (butanol extractable and re-extractable in NaOH). The sample contained 1.18 μc.; 0.98 μc. was recovered between 4 and 34 cc. Diiodotyrosine and monoiodotyrosine were the main components, together with a small quantity of thyroxine.

to thyroxine (Fig. 6). Paper chromatograms and radioautographs of the latter fraction also indicated strong mono- and diiodotyrosine spots, and a weak thyroxine spot.

The recovery of radioactivity in three effluent bands averaged 99.7 per cent (93 to 106 per cent) of the total added to the column for chromatograms on cellulose, and 84 per cent (79.2 to 88 per cent) for those on starch. The percentage recovery of I^{131} from starch was apparently not modified by the addition of amino acid carriers. On counting the starch column linearly from top to bottom directly after the emergence of monoiodotyrosine, it was found that small amounts of I^{131} were detectable throughout the length of the column, with a larger amount present in a band 3 to 4 cm. from the top (Fig. 1). From the relationship,

predicted effluent volume (cc.) = volume emerged at time of counting column $\times \frac{\text{length of column}}{\text{position of band in column (cm. from top)}}$,

it was estimated that this band would emerge at an effluent volume of 200 to 240 cc. This I^{131} adsorbed near the top of the column accounted for most of the difference in the radioactivity between the sample chromatographed and that contained in the three major effluent peaks. The addition to the starch column of 50 to 500 gamma of I_2 labelled with I^{131} (prepared by extracting with chromatographic solvent an acid aqueous reaction mixture of iodate and labelled iodide) resulted in the greater part of the radioactivity moving slowly as a brown band, the rate of migration of which was very close to that of the residual band from a thyroid hydrolysate chromatogram; however, 13 to 20 per cent of the added I^{131} travelled rapidly and emerged with the solvent front at approximately 5 cc., and tailed off gradually. Distribution studies on the rapidly moving compound indicated that it was not iodine, iodide, or iodate. Decomposition to iodine of some iodine-containing material in the thyroid hydrolysate which was chromatographed, and emergence of part of this with the solvent front, may be a factor in the discrepancy observed between I^{131} in the first effluent band and the descending limb of thyroxine determined colorimetrically. Quantitatively, however, this would account for only a small fraction of the observed difference. Equal percentage recoveries were obtained when both the thyroxine and the monoiodotyrosine and diiodotyrosine fractions were run separately; in each case a band was detectable in the column moving at approximately the same slow rate as iodine, and accounting for the incomplete recoveries in the major effluent bands. The incorporation in the solvent of thiodiglycol (0.5 per cent), which protects methionine from oxidation during chromatography (19), and of the reducing agent thiourea (0.1 per cent) did not result in higher recovery.

Re-use of the chromatographic columns prepared as described was found to be possible. Chromatograms have been made with one cellulose column six times and with starch twice, with little loss of resolving power as judged by the emergent I^{131} curves. Cellulose columns have proved more suitable for re-use because virtually all of the added I^{131} appears within the three effluent bands, and hence there is no interference on subsequent runs from I^{131} retained in the column. The first chromatogram developed on a freshly prepared cellulose column, particularly if carrier amino acids were not added, on occasion showed a distortion of the thyroxine band, in that it was poorly separated from diiodotyrosine or emerged with two peaks. The reason for this behavior was not clear.

DISCUSSION

From the results described, it would appear that the qualitative and quantitative analysis of the iodine-containing constituents of the thyroid by chromatography on columns is a feasible procedure. Column chromatography provides certain advantages as compared with paper chromatography. Larger quantities of material can be resolved,[2] an advantage in preparative work. Secondly, the effluent bands emerge in a form which is more readily subjected to other chemical procedures. Analysis of the symmetry of the effluent bands provides some evidence as to homogeneity and, if resolution is incomplete, selection of the least contaminated portions of the band for further study is possible. Column chromatograms are more readily subjected to quantitative study than paper chromatograms.

Each of the two types of columns studied presents certain advantages over the other. The reproducibility and high resolving-power of the starch column make it preferable for qualitative analysis, but the failure of the solvent system employed to retard thyroxine and the occurrence of decomposition are drawbacks. The emergence of thyroxine with the solvent front means that it would not be separated from other iodine-containing substances that might behave similarly; although this is probably of little consequence in experiments dealing with the thyroid gland, it might be important in the chromatographic study of iodinated proteins in which acid-insoluble, butanol-extractable iodine appears to include compounds in addition to thyroxine (4). Maximal resolution on starch columns occurs after the passage of approximately five-column volumes (V) of solvent (25); in the system studied, diiodotyrosine emerges at 3V and monoiodotyrosine at 5V. The favorable features of cellulose columns as used here are the excellent recoveries, minimal decomposition, and ease of preparation and operation. In addition, thyroxine emerges after the solvent

[2] A cellulose column 50×0.95 cm. can readily resolve 3 mg. each of thyroxine, diiodotyrosine, and monoiodotyrosine.

front (the R value (26) being approximately 0.75) and with less asymmetry than on a starch. Disadvantages of cellulose are the changes in the properties of the solvent system with time and the inconstancy of the absolute positions of the peaks. In the butanol-acetic acid-water solvent system the three iodinated amino acids emerge at between 1.25 and 2V. When this solvent is used for paper chromatograms a reduction in the water content of the solvent exerts a retarding effect on all constituents, especially diiodotyrosine and monoiodotyrosine (15). Butanol saturated with water moves thyroxine at a satisfactory rate on paper (23). One might predict that greater resolution of thyroxine and substances with similar distribution ratios might be achieved on cellulose columns by the use of butanol solvents containing little water. The emergence of monoiodotyrosine and diiodotyrosine might then be unduly prolonged but by running aliquots of the sample on each of two columns with solvents of different water content, satisfactory resolution of both types of compound might be achieved.

Although the modifications of the Leland and Foster butanol extraction procedure (27) applied to alkaline hydrolysates of thyroid have given reasonably good thyroxine values, it would appear that what has generally been considered the "diiodotyrosine fraction" contains also monoiodotyrosine and may not be completely free of thyroxine. Paper chromatography has thus far provided almost the only means for separating and estimating the monoiodotyrosine content of the gland by a procedure involving iodine determination of the appropriately excised segment of paper (10). Chromatography on columns, with pooling of the effluent fractions corresponding to monoiodotyrosine, and iodine determination performed on the pool, would appear to be an alternative method.

The application of column chromatographic methods to the study of the constitution and analysis of iodinated proteins may be helpful. Reference has already been made to the apparent lack of correlation between thyroxine content and biologic activity on the one hand, and acid-insoluble, butanol-extractable iodine on the other, the latter generally far exceeding the former in amount. Resolution of the iodine-containing constituents of a hydrolysate might be possible by passage through a column, and estimation of the nature and quantity of each component might be made by observation of the position and magnitude of the effluent bands. These could be determined by iodine analysis or by such colorimetric procedures as those of Winikoff and Trikojus (28), and of Roche (29) for thyroxine, diiodotyrosine, and monoiodotyrosine. On starch, monoiodotyrosine and tyrosine are so completely distinct from each other that the Millon reaction applied to the effluent fractions might be used to detect the former. Analysis might be facilitated by addition to the hydrolyzed protein sample

to be fractionated, of a thyroid gland hydrolysate from a rat previously injected with I^{131}, and observation of the correspondence between the effluent curves of I^{131} and of the colorimetrically determined bands.

A preliminary study of the applicability of these methods to the study of iodinated proteins has been made by determining the nature of the iodinated products formed in the enzymatic iodination system described by Keston (30). Unpasteurized milk was incubated with xanthine, phosphate buffer and iodide labelled with I^{131}; approximately 5×10^{-4} moles of iodine were present per mole of tyrosine in the milk casein. After iodination was complete, alkaline hydrolysis of the trichloroacetic acid-precipitated protein followed by butanol extraction was performed, as described for thyroid hydrolysates, and the extract chromatographed on cellulose. Approximately 70 per cent of the total bound I^{131} was found to be in monoiodotyrosine, with smaller amounts in thyroxine, in diiodotyrosine, and probably in a third, unidentified compound. The predominance of monoiodotyrosine is consistent with the results of Roche (31) and of Herriot (32) in iodination of proteins with small quantities of iodine.

SUMMARY

Thyroid hydrolysates containing labelled iodinated amino acids have been prepared from the glands of rats receiving radioactive iodine. Chromatography of these preparations by elution development on columns of starch and cellulose indicated thyroxine, diiodotyrosine, and monoiodotyrosine to be the predominant organic iodine compounds of the thyroid. Of the total organic I^{131}, 35 to 45 per cent was present as thyroxine, 40 to 45 per cent as diiodotyrosine, and 15 to 20 per cent as monoiodotyrosine. Methods of preparation and operation of the columns and the advantages and limitations of each type are described. The applicability of the column chromatographic methods to the analysis of natural and artificial thyroprotein is discussed.

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THE EFFECT OF THYROTROPIN ON THE RELEASE OF HORMONE FROM THE HUMAN THYROID*†

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INTRODUCTION

THE thyrotropic hormone of the anterior pituitary gland (TSH) stimulates the thyroid gland. An increase in metabolic rate in patients injected with impure TSH was observed by Eitel (1), Thompson, *et al.* (2), Sharpey-Schafer, *et al.* (3), and others. Similar results have been obtained in various laboratory animals. It has not been clear, however, which of the various stages in the metabolic pathway of iodine through the thyroid are primarily stimulated by TSH and which may be seemingly stimulated only because the preceding step was altered. Leblond and Süe (6) suggested that TSH might act as a general thyroid-cell stimulant, increasing the native synthetic processes of the thyroid by enhancing proportionately each of the steps in the manufacture, storage, and secretion of thyroid hormone. TSH is known to increase the inorganic iodide content of the thyroid in man and other animals, to increase the rate of organic binding of iodine and to effect a discharge from the chick thyroid of previously administered radioactive iodine (I^{131}). Very recently Vander-Laan and Greer (8) have found that the rate of loss of I^{131} from the rat thyroid is increased by injecting TSH when hormone synthesis by the gland is blocked with propylthiouracil.

In the last analysis, the rate of release of stored thyroid hormone from the gland controls the metabolic state of the organism. The present study concerns this release from the human thyroid under the influence of TSH when the factor of hormone synthesis has been controlled.

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METHOD

Six patients with typical thyrotoxicosis were chosen for this study. Initially each patient was given orally 100 to 265 microcuries of radioiodine, (I^{131}), labeling 10 micrograms of inert iodide (I^{127}) in the form of NaI. *In vivo* counting rates were determined twice daily throughout the experiment by means of a platinum-screen cathode Geig- Mueller (G-M) counter placed 20 cm. from the neck. Radioactivity other than that in the thyroid was reduced by means of a lead shield placed around the counter. All urines were collected, and the amount of radioiodine excreted daily was determined by measurements in a beaker surrounding a copper-cathode G-M counter. The serum protein-bound iodine (PBI), the basal metabolic rate (BMR), and the serum protein-bound radioiodine (labeled serum PBI) were measured once or twice during each of the three periods of the study. Each period was either four or five days. In the first, or control period, the 48-hour thyroidal accumulation and kidney excretion of labeled iodine and the subsequent rate of loss of labeled iodine from the thyroid were established. During the second, or 1-methyl-2-mercaptoimidazole (MMIA)[1] period, the rate of loss of radioactivity from the blocked thyroid was measured. In the third, or TSH period, the rate of loss of radioactivity from the blocked thyroid under TSH stimulation was studied. Finally, while the patient was still receiving MMIA, a second tracer dose of 100 microcuries of I^{131} labeling 10 micrograms of I^{127} was given and and the 48-hour thyroidal accumulation and urinary excretion were measured for comparison with control measurements. This comparison served as an index of the effectiveness of the MMIA block.

The blocking agent, MMIA, is an antithyroid drug used by Astwood *et al.* (9), and considered the most potent yet available. The doses varied from 5 to 20 mg. every six hours. The TSH was a lyophilized thyrotropic hormone preparation[2] given in sterile saline in doses of either 12.5 or 25 mg. every twelve hours.

All *in vivo* measurements over the thyroid were corrected for resolving time, counter background, and the 8-day physical decay of the I^{131}. These measurements were placed on an absolute scale of per cent of administered labeled iodine retained in the thyroid by assuming that at forty-eight hours

[1] The 1-methyl-2-mercaptoimidazole was made available through the courtesy of Dr. D. C. Hines of Eli Lilly & Co. Each tablet contained 5 mg. of the pure substance.

[2] The thyrotropic hormone preparation was made available through the courtesy of Dr. John R. Mote of Armour & Co. Each vial contained 25 mg. of Lot H 71608 purified thyrotropic hormone assaying 4.5 Evans units per mg. Adrenocorticotropin was present on a weight basis as 10 per cent of La-I-A. Gonadotropins were practically absent; and growth hormone, oxytocic and pressor substances, and prolactin were very low.

after the administration of labeled iodide it had either been excreted in the urine or was held in the thyroid. Because of the rather small urinary excretion during this 48-hour period the scale can be determined fairly accurately. Although most investigators agree that this assumption is approximately valid, a significant amount of labeled iodine may be retained in the blood at forty-eight hours, and some labeled iodine may be excreted by routes other than the urine. Serum measurements suggest that as much as 11 per cent of the radioactivity may be present in the extracellular fluid at this time. This is not of immediate importance, since the rate of release of labeled iodine from the thyroid, not the absolute amount of labeled iodine released, is the quantity desired.

Errors occur in the positioning of the counter relative to the thyroid gland, in variations of counter sensitivity, and in statistical errors of counting. The first of these is undoubtedly the most important. The total error of each measurement is estimated to be 5 per cent or less.

The amount of labeled iodine in a day's collection of urine was determined by comparing the activity of a sample of the urine collection with that of an aliquot of a standard solution identical with the dose of radioiodine administered to the patient. Errors arise in collecting the urine and in the counting statistics. The former was minimized by hospitalizing all patients during this study. The total error in determining the daily excretion of labeled iodine is about 3 per cent.

The concentration of serum PBI was determined by a modification of the method of Barker (10) and the concentration of labeled iodine in the various serum fractions was determined by means of a dip counter.[3] The activity of a 4.5-cc. sample of serum was compared with the activity of an aliquot of the standard solution, and the result was expressed in terms of per cent of the labeled iodine per liter of serum. This was called the "total" serum concentration of labeled iodine. The sample of serum was then completely cleared of protein, using a 25 per cent solution of trichloracetic acid, and the activity in the supernatant fluid was measured. The difference between the "total" and the "supernatant" concentrations of labeled iodine was called the concentration of labeled serum PBI.

RESULTS

The effect of TSH was determined by measuring the rate of release of labeled iodine from the thyroid gland. The rate of release was first studied in the absence of any therapy, and was found to be constant. This is well supported by the theoretical analysis of Oddie (12), who found the rate

[3] The dip counter was designed by Dr. A. K. Solomon (11), and was used through his courtesy.

constant for the release of hormone from the thyroid to be the controlling factor after the second day. This assumption has been verified by a number of workers who have actually observed the release of labeled iodine over a period of weeks (13 and 14), and by ourselves. Figure 1 contains the retention data[4] for a patient who received 10 millicuries of radioiodide for

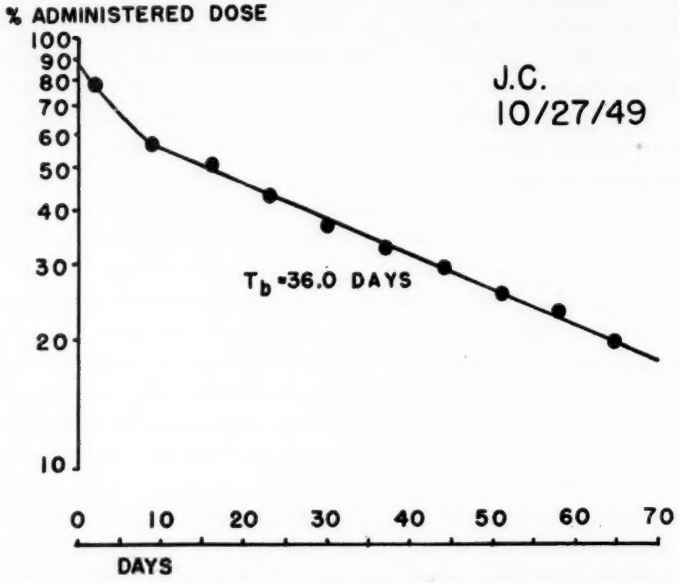


FIG. 1. Biologic decay of I^{131} in a thyrotoxic subject given 10 millicuries of I^{131} at zero time. Abscissa: time in days. Ordinate: percentage of administered dose. T_b: biologic half-period in days. The curve has been corrected for physical decay and resolving time.

the treatment of thyrotoxicosis. After the first week the retention curve followed an exponential relationship over a period of more than one month. The changes occurring during the first week were probably due to radiation destruction and were not present in the patients observed in the present study.

The effect of MMIA alone on the retention curve of labeled iodine in the thyroid was determined in 1 patient (Fig. 2). At the start, a dose of 10 micrograms of iodine in the form of sodium iodide labeled with 250 microcuries of I^{131} was administered orally. The rate of release with no therapy was observed over a control period until the retention curve was established. The biologic half-period was 32.3 days. Then the patient

[4] The data for Figure 1 were kindly loaned by Dr. Farahe Maloof.

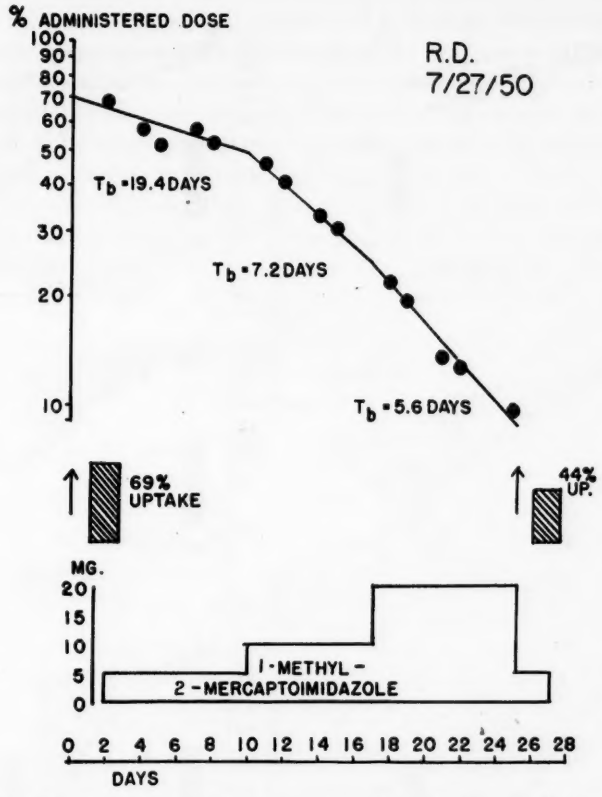
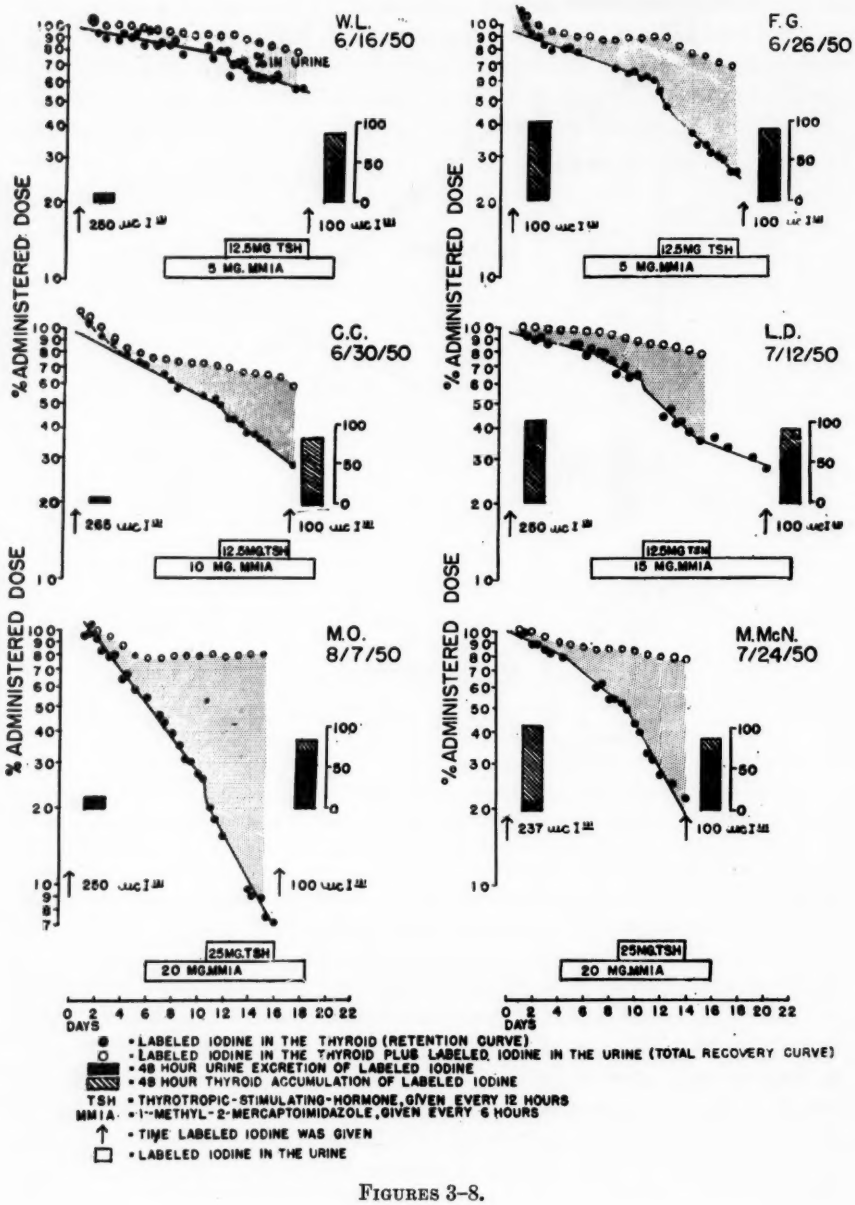


FIG. 2. The effect of a thyroid-blocking agent on biologic decay of I^{131} in a thyrotoxic subject. A tracer dose of I^{131} was given at zero time and at twenty-five days. The upper ordinate represents the percentage of the administered dose remaining in the thyroid. T_b: biologic half periods. The points are corrected for physical decay. The lower ordinate is milligrams of the drug given every six hours. The shaded areas represent the percentage of the administered tracer dose retained at forty-eight hours.

received 5 milligrams of MMIA every six hours and a biologic half-period[5] of 19.4 days, corresponding to an excretion of 3.6 per cent per day,[6] was noted. On 10 milligrams of MMIA there was a new exponential slope with a biologic half-period of 7.2 days and a calculated excretion of 9.6 per cent per day. When the dosage of MMIA was increased to 20 milligrams every

[5] This is the period of time in days required for the thyroid to lose 50 per cent of the labeled iodide it contains at any time after original equilibrium has been established.

[6] These excretion data were calculated on the basis of the formula presented in the Appendix.


W.L.
6/16/50
F.G.
6/26/50
C.C.
6/30/50
L.D.
7/12/50
M.O.
8/7/50
M.McN.
7/24/50
% ADMINISTERED DOSE
% IN URINE
250 μμc I¹³¹
100 μμc I¹³¹
100 μμc I¹³¹
265 μμc I¹³¹
250 μμc I¹³¹
237 μμc I¹³¹
12.5MG TSH
5 MG. MMIA
10 MG. MMIA
15 MG. MMIA
25MG.TSH
20 MG.MMIA
DAYS
• LABELED IODINE IN THE THYROID (RETENTION CURVE)
• LABELED IODINE IN THE THYROID PLUS LABELED IODINE IN THE URINE (TOTAL RECOVERY CURVE)
• 48 HOUR URINE EXCRETION OF LABELED IODINE
• 48 HOUR THYROID ACCUMULATION OF LABELED IODINE
TSH • THYROTROPIC-STIMULATING-HORMONE, GIVEN EVERY 12 HOURS
MMIA • 1-METHYL-2-MERCAPTOIMIDAZOLE, GIVEN EVERY 6 HOURS
• TIME LABELED IODINE WAS GIVEN
• LABELED IODINE IN THE URINE

FIGURES 3–8.

six hours, the new exponential curve had a biologic half-period of 5.6 days and a daily calculated excretion of 12.4 per cent.

The results obtained on the 6 thyrotoxic patients are presented in Figures 3–8 and in Tables 1 and 2. In Figures 3–8, at the start of each control period the 48-hour urinary excretion and in 3 instances thyroidal accumulation of labeled iodide are indicated by bar graphs, and the excretion values are given in Table 3. In all cases these measurements fell within the accepted thyrotoxic range for the method used (15), *i.e.*, 0–40 per cent of the administered activity excreted, and 60–100 per cent accumulated.

TABLE 1

Patient	Biologic half-period (days)				Excretion (% of retained labeled iodine/day)					
					Control period		MMIA period		TSH period	
	Control	MMIA	MMIA-TSH	MMIA	Calc.	Measured	Calc.	Measured	Calc.	Measured
W.L. 5 mg. MMIA 12.5 mg. TSH	53±35	27.2±9.0	18.4±4.4		1.3	0.1	2.5	1.2	3.8	2.5
F.G. 5 mg. MMIA 12.5 mg. TSH	20.3±6.1	17.3±3.6	6.63±0.41		3.4	1.6	4.0	4.4	10.4	7.0
C.C. 10 mg. MMIA 12.5 mg. TSH	12.6±2.1	12.1±1.7	8.09±0.57		5.5	1.5	5.7	3.9	8.6	6.7
L.D. 15 mg. MMIA 12.5 mg. TSH	25.4±4.5	8.95±1.30	5.64±0.51	12.60±2.77	2.7	1.9	9.8	3.0	12.3	8.6
M.O. 20 mg. MMIA 25 mg. TSH	5.41±0.41	3.92±0.23	3.22±0.15		12.8	3.2	17.7	18.5	21.5	29.3
M.McN. 20 mg. MMIA 25 mg. TSH	11.6±2.0	6.54±0.78	3.55±0.21		6.0	2.1	10.6	8.2	19.5	16.3

Similar data obtained after completion of the TSH period, while the patients were still receiving MMIA, are also shown. In 5 of the 6 cases these latter measurements were within the euthyroid range, *i.e.*, 44–87.8 per cent of the administered activity excreted (15). Although no instance of complete inhibition of thyroidal iodine accumulation was found, significant inhibition was noted in 5 of these patients. This was most complete with the higher dosage of MMIA (patients M.O. and M.McN.). Patient C.C., however, excreted only 10 per cent in the urine while taking MMIA, as compared with 6 per cent without therapy. The biologic half-periods during the control period, as calculated from the data of the control phase of the

study, are presented in Table 1. These and the other slopes were calculated by the method of least squares.

The biologic half-periods, as determined by *in vivo* measurements, were not significantly altered from those present during the control periods in patients receiving 5 and 10 mg. of MMIA every six hours (patients C. C., F. G. and W. L.). In contrast, the 3 patients who received 15 or 20 mg. of MMIA every six hours (patients L.D., M.O. and M.McN.) demon-

TABLE 2

Patient	Dose of MMIA (mg./6 hrs.)	Period	BMR	PBI of serum (micrograms %)	Total I^{131}* of serum (% dose/L)	PBI^{131}** of serum (% total I^{131})	Eosinophils (no./cu. mm.)
W.L.	5	Control	+23, +30	13.5			
		MMIA					
		TSH	+18, +23	14.0, 14.8			
F.G.	5	Control	+29, +17	16.1			
		MMIA	+15, + 4				
		TSH	+ 3, − 7	7.8			
C.C.	10	Control	+64, +65	24.5			
		MMIA	+66	17.0			
		TSH	+51, +46	10.8			
L.D.	15	Control	+49, +50	14.5			
		MMIA	+34, +34	10.0	0.8, 0.8	100, 80	198, 240
		TSH	+32, +28	13.3	0.9, 1.2	100	328, 295
M.O.	20	Control	+57, +57	18.2	2.4	100	395, 385
		MMIA	+58, +38	10.3	1.6, 1.5	100	309, 329
		TSH	+24, +17	9.2, 7.3	0.8	100	340, 473
M.McN.	20	Control	+41, +54	22.0, 24.2	1.5	50	573
		MMIA	+41, +27	14.1	0.9, 0.9	100	841
		TSH	+51	12.5	0.8, 0.8	100	802, 938

* Total I^{131} = concentration of serum labeled iodine, % dose/liter of serum.
** PBI^{131} = concentration of serum labeled protein-bound iodine, % of total I^{131}.

strated significant changes ($P<0.05$) in the exponential slopes of the retention curves and in the biologic half-periods during the MMIA periods as compared to the control periods. This is in accord with Figure 2.

During the control period, the urinary excretion of labeled iodine calculated[7] from the biologic half-period was considerably higher than the values actually observed. During the MMIA period the calculated excretions remained higher than the measured values in 4 of the 6 patients, but the discrepancy was not as large as in the control period. The same was true for 5 of the 6 patients during the TSH period. These data are seen in Table 1, in which the per cent daily excretion of labeled iodine is presented for the control, MMIA, and TSH periods. These values were obtained by

[7] See Appendix.

dividing the amount excreted in the urine by the amount of the administered quantity remaining in the thyroid on that day. It should be pointed out that this quantity remained nearly constant over each of the periods, and therefore can be averaged over each. The absolute amount of labeled iodine excreted per day decreases approximately exponentially over each period, and thus the average would depend on the duration of the period. The calculated excretions determined from the biologic half-periods of the retention curves of Figures 3–8 are also presented in Table 1.

TABLE 3

Patient	48-Hour excretion (% of dose)		ϵ_R
	Control	MMIA block	Re-utilization fraction
W.L. 5 mg. MMIA	9	35	0.77
F.G. 5 mg. MMIA	12	57	0.25
C.C. 10 mg. MMIA	6	66	0.73
L.D. 15 mg. MMIA	8	65	0.75
M.O. 20 mg. MMIA	17	71	0.37
M.McN. 20 mg. MMIA	9	72	0.53

The total recovery curve in Figures 3–8 represents the sum of the labeled iodine present in the thyroid and cumulatively excreted in the urine. The area between the total recovery and the retention curves represents the urinary excretion of labeled iodine. If the total recovery were always 100 per cent of the administered iodine, the recovery curve would describe a line parallel to the abscissa. From 16 to 58 per cent of the administered labeled iodine appeared in the urine during the control and MMIA periods, with 24 to 76 per cent remaining in the thyroid gland. This leaves 8 to 25 per cent of the labeled iodine, the difference between the theoretical and the actual recovery curves, unaccounted for.

The immediate effect of TSH on the release of labeled iodine from the

thyroid is dramatic. TSH produced a sharp increase in the rate of release of labeled iodine from the thyroid of each subject. This was observed within the first twelve hours in 4 patients (W.L., F.G., C.C., and M.O.). In each of the 6 patients the retention curve assumed a new exponential slope on TSH. In 5 of these the change was significant ($P<0.05$). The observed change in the half-period was pronounced in 5 of the subjects and was not an apparent function of the MMIA or TSH dosage in the dose range used. The measured urinary excretion during the TSH period rose above previous measurements in each patient. During TSH administration, just as in the MMIA period, this excretion remained less than the urinary excretion calculated from the retention curve, except in patient M.O. As mentioned before, in patient M.O. the short biologic half-period during the control period and the low absolute counting rate during the later periods may account for this deviation.

The total recovery curves continued to decline steadily during the TSH periods. From 24 to 66 per cent of the administered labeled iodine appeared in the urine by the end of the TSH period, with 7 to 56 per cent remaining in the thyroid. This left 20 to 37 per cent remaining to be accounted for at the end of the study.

The BMR determinations (Table 2) were all within the accepted thyrotoxic range during the control period. During the MMIA period the BMR dropped significantly in all 6 subjects and reached the euthyroid range in patient F.G. These values continued to fall during the TSH period in each instance except for patient M.McN. The values were still in the hyperthyroid range, however, in all except F.G.

The concentration of PBI in the serum was within the usual thyrotoxic range in all of the patients during the control period (Table 2). In 4 of the 6 patients this value decreased during the MMIA period, none reaching the euthyroid range. During the TSH period these values decreased further in 4 of the 6 patients, reaching euthyroid levels in patients F.G. and M.O. In patient W. L. there was no significant change in the TSH period as compared with the control period, and in patient L.D. the serum PBI concentration increased from the previous MMIA-period level to that present originally. The concentration of labeled serum PBI showed the same trend as the chemically determined PBI and constituted approximately 100 per cent of the total serum labeled iodine in each instance. The circulating blood eosinophil count was within the accepted normal range in 2 of 3 patients and was high in the third patient. The count rose slightly during the MMIA and TSH periods in each instance.

DISCUSSION

In the thyrotoxic human subject TSH increases the rate of release of

thyroid hormone from the thyroid hormone store, independently of its effect on iodide accumulation by the gland. This hormone store is presumably within the thyroid acinar colloid. Both the biologic half-period and the measured urinary excretion of labeled iodine reflect this increased release of labeled hormone during the administration of TSH. Since in each case ten days elapsed between the administration of the first dose of labeled iodine and the start of the administration of TSH, one can be reasonably certain that all or nearly all of the thyroidal labeled iodine was in the form of thyroid hormone by the beginning of the TSH period.

Since MMIA inhibits the incorporation of iodide into an iodo-protein complex, the effect of TSH on the rate of hormone *formation* by the thyroid was therefore minimized. Although MMIA inhibits re-utilization of labeled iodide, the fact that none of the subjects collected less than 10 per cent of a tracer dose of labeled iodine during MMIA therapy suggests that some organic binding of iodine persisted. In patient L.D. the administration of 2 grams of KSCN forty-eight hours after the second tracer of labeled iodide failed to decrease the counting rate over the thyroid during the subsequent three hours, suggesting that in this patient the labeled iodine which was collected by the blocked thyroid, was held as hormone-iodine (16).

The altered rate of release of labeled iodine from the thyroid was evident within twelve hours after the first injection of TSH in at least 4 of the cases, and this altered rate was shown to revert to normal within twelve hours after discontinuing TSH in patient L.D. According to Stanley *et al.* (5), the effect of a single injection of TSH on the iodide space of the thyroid lasts from three to five days. Keating and Rawson (7) working with chick thyroids and repeated injections of TSH found a marked increase in acinar cell height within twenty-four hours after the first injection, while the thyroid weight increased moderately within this period and reached a maximum only after seventy-two hours. Following a single injection of TSH the tendency for the chick thyroid to increase in weight disappeared after four days, the rise in mean acinar cell height was lessening but present after four days, and the rise in total collection of labeled iodine was still increasing after four days. These same authors found an increase in the rate of loss of labeled iodine from the untreated chick thyroid within twenty-four hours after an injection of TSH: after seventy-two hours the thyroids had lost 96 per cent of the labeled iodine originally accumulated, whereas control thyroids had lost only 50 per cent. Leblond (4) suggested that TSH stimulated thyroid cells both in regard to cell division and to general metabolic functions since, as a result of TSH, the capacity to collect iodine increased more than could be explained by the increase in thyroid mass. These findings, together with

those recorded in this study, support the thesis that TSH affects various functions of the thyroid cell differently. Otherwise it seems difficult to explain why, when the effect on hormone release appears to last no more than twelve hours, TSH should continue to cause an increase in iodine accumulation capacity for an additional 60 to 108 hours.

Certain actions of TSH on activities other than the release of labeled hormone were also observed. The BMR determinations and the concentration of serum PBI, stable and labeled, decreased in 5 of the 6 patients during TSH stimulation. This is in contrast to the findings of Thompson, *et al.* (2), and Sharpey-Schafer, *et al.* (3), who found that TSH uniformly produced a rise in BMR. Their subjects, however, were not under treatment with an antithyroid drug, and consequently were able continually to replenish their hormone stores. The increased rate of release of hormone from the thyroid induced by TSH probably cannot be observed as an elevation of hormone concentration in the peripheral blood if hormone synthesis is depressed, especially since the toxic thyroid has low hormone stores. In this regard it should be clear that "rate of release" is relative to the quantity of hormone store present at the time, and as such is not a measure of absolute quantity delivered from the gland, but is only a measure of glandular activity.

Only 1 of the 6 patients had any noteworthy clinical response to TSH. This patient had a fall in BMR and serum PBI concentration during the MMIA period, a general increase in sense of well-being, and a decrease in all symptoms, *i.e.*, the same response noted by the other patients during this period. During the TSH period she rapidly re-exhibited marked emotional instability and hyperactivity, to an even greater degree than had been present just prior to her hospitalization. In addition, she complained for the first time of tearing of her eyes and of a choking sensation in her neck. Her eyes became more prominent and puffy and auricular fibrillation was observed. A transient attack had been reported earlier but had not been observed in the hospital. The BMR dropped from plus 41 per cent and 54 per cent in the control period to plus 27 per cent in the MMIA period and rose again to plus 51 per cent under TSH stimulation. The serum PBI concentration dropped during the MMIA period and continued to fall in the TSH period. The subjective and objective changes promptly disappeared or reverted to normal after the end of the TSH period.

The manufacturers of the TSH considered that the material was contaminated to the extent of 10 per cent with ACTH-like substances. Therefore, the circulating eosinophils were counted during each of the three periods in 3 patients. In these subjects the control counts were within the normal range, there were no changes during the MMIA period, and the counts either remained the same or rose by the end of the TSH period.

During the three periods the calculated urinary excretion was almost always higher than the measured values (Figures 3–8 and Table 1). If all the labeled iodine were either retained in the thyroid or excreted in the urine, this curve should have the constant value of 100 per cent. If an appreciable amount of labeled iodine were present in an extrathyroidal locus, this curve would drop below 100 per cent for the first few days, but would gradually return to that value with the turnover of both the thyroidal and extrathyroidal labeled iodine. However, only if there is a route of excretion from the body other than the urine will the dashed curves of Figures 3–8 follow the steady downward trend noted in all 6 cases studied. It must be concluded that a considerable portion, 15 to 40 per cent, of the labeled iodine released from the thyroid in organic form is excreted by alternative routes. This rate of loss of labeled iodine by alternative routes appears to be proportional to the rate of loss via the urine. Albert and Keating (17) found considerable amounts of labeled iodine in the feces of their subjects given labeled thyroxin. Very possibly this was the route of excretion of the missing iodine in our 6 subjects.

During the control period the calculated values of the urinary excretion of labeled iodine are greater than the measured values by a factor considerably larger than that found for the other two periods. Part of this discrepancy arises from the limiting assumption made earlier, *i.e.*, that the extrathyroidal labeled iodine is negligible forty-eight hours after the ingestion of the labeled iodide. The present data suggest that this assumption may not be entirely true. The serum concentration of labeled PBI is approximately 1 to 2 per cent of the administered dose per liter of serum on about the third day. Since the PBI space is several liters, the extrathyroidal labeled iodine is appreciable within the first few days following the administration of labeled material.

An estimate of the amount of the released iodine re-utilized by the thyroid may be obtained from the measured biologic half-periods, and from the per cent uptake of labeled iodide by the blocked and unblocked gland. The calculation used to obtain the per cent re-utilization is given in the appendix. These fractions are shown in Table 3. With the high uptakes of radioiodide by the thyroids of these subjects one might wonder why these values are not equally high. One explanation may be found in the recent demonstration by Rall (18) that organically bound iodine is excreted in the urine of thyrotoxic subjects. Presumably such iodine would not be available for reutilization. The fecal loss previously mentioned might be another source of discrepancy in the calculation.

SUMMARY

1. The administration of 1-methyl-2-mercaptoimidazole caused an

increase of the biologic decay rate of previously fixed labeled iodine from the thyroids of 3 of 6 thyrotoxic subjects. The effectiveness of the drug in increasing the excretion of a tracer dose of radioactive iodine was demonstrated in all cases.

2. The additional administration of thyrotropin caused an increase or a further increase in the biologic decay rate in all 6 subjects. Thus, thyrotropin causes an increased release of thyroid hormone independently of, and in addition to, its effect on iodide accumulation.

3. With one exception the thyrotropin caused no aggravation of the thyrotoxicosis in these 6 subjects who were under the influence of a potent antithyroid drug.

4. Various implications of these results are discussed.

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APPENDIX

Calculation of Excretion

For the immediate period after administration, the metabolic fate of labeled iodine is quite complex. The iodide will quickly appear in the blood, be cleared by the thyroid, and be converted into organic iodine. Both the organic and inorganic iodine will be released to the blood and eventually excreted. At the end of two days following administration the system may be represented by a much simpler model. At this time most of the iodide in the blood will have been cleared, and the major portion of the iodine in the body will be present in organic form in the thyroid. If the normal iodine equilibrium has not been altered, a fundamental assumption in any tracer experiment, the rate of release of the labeled hormone will be constant and will be equal to the rate of release of unlabeled hormone. This fraction will be designated by k. However, a part of the released hormone will be re-utilized by the unblocked gland. If ϵ_R is this fraction and I is the quantity of labeled iodine in the thyroid, the rate of release of labeled iodine will be:

$$\frac{dI}{dt} = -(1 - \epsilon_R)kI$$

and the general relation is found:

$$I = Io e^{-(1-\epsilon_R)kt}$$

where: I = amount of labeled iodine at time t
Io = amount of labeled iodine at time $t = o$
e = base of natural logarithms, 2.718
R = fraction of released hormone that is re-utilized
k = fraction of thyroid hormone released per day
t = time in days

If the added assumption is made that the extrathyroidal labeled iodide is negligible for times greater than two days, the excretion of labeled iodine should equal the release from the thyroid, less the amount re-utilized. In the present report, excretion, E, is defined as the percentage of the retained labeled iodine leaving the body each day. Thus:

$$E = -\frac{100}{I}\frac{dI}{dt} = 100(1 - \epsilon_R)k$$

The biologic half-period, Tb, is equal to

$$\frac{0.693}{(1 - \epsilon_R)k} \quad \text{and} \quad E = \frac{69.3}{Tb}.$$

It is possible to calculate the re-utilization fraction from the excretion data of the blocked and unblocked gland. It will be assumed that the release constant, k, is the same in the two cases, and that the re-utilization in the blocked gland is decreased from that of the unblocked gland by the ratio of the corresponding labeled iodide uptakes. Then:

$$Eo = 100(1 - \epsilon_R)k$$

$$Eb = 100\left(1 - \frac{Ub}{Uo}\epsilon_R\right)k$$

where Ub and Uo are the labeled iodide uptakes in the blocked and unblocked glands. The re-utilization fraction is then found to be:

$$\epsilon_R = \frac{1 - \frac{Eo}{Eb}}{1 - \frac{Ub}{Uo}\frac{Eo}{Eb}} \cdot \frac{1 - \frac{Tb}{To}}{1 - \frac{Ub}{Uo}\frac{Tb}{To}}$$

where Tb and To are the biologic half-periods of the blocked and unblocked glands.

ANALYSIS OF TECHNIQUES FOR THE DETERMINATION OF THYROID FUNCTION WITH RADIOIODINE*†

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INTRODUCTION

THE advent of radioiodine has increased greatly the quantitative information which may be obtained concerning the physiology of the thyroid gland. In addition to supplanting the techniques for measuring the equilibrium constants of the gland, such as the percentage utilization of the daily intake of iodide, radioiodine allows the dynamic measurement of characteristics such as the rate of accumulation of iodide by the gland and the rate of release of hormone. These measurements would be virtually impossible to obtain by other techniques and they are playing an increasingly important role in the study of thyroid physiology. The dynamic measurements of thyroid function form the major topic of discussion of this paper.

In general, a radioiodine test includes the administration of radioiodine (usually in the form of iodide), measurement of radioiodine content of the thyroid by means of external detection, measurement of radioiodine content of serum and urine, and mathematical analysis of the data. This mathematical analysis may consist of nothing more than correcting for the physical decay of the radioiodine or comparison with a standard, or it may involve plotting of data and more complicated numerical procedures. The result is then compared with data of control groups of patients of the various categories of thyroid status, and a diagnosis is made.

Two criteria will be postulated as essential for a radioiodine diagnostic test:

1. The test should be indicative of thyroid state.

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2. The test should measure a fundamental parameter of the thyroid. The first criterion requires little justification, since it is the primary criterion for most of the commonly used tests. It is clear that the test must give a statistically significant result as to the thyroid status of the patient in order to be of value to the clinician. The second criterion is by no means as clear, and requires some justification. If only one thyroid test were employed, there would be little argument for the second criterion. It is becoming increasingly common, however, for the clinician to require two or even more independent radioiodine tests in the formulation of his diagnosis, particularly in borderline cases. In general, only if these tests measure fundamental physiologic parameters will the sum of the data provide more information than that of an individual test. As increased knowledge is obtained of the many functions of the thyroid gland, these measurements will serve an increasingly important role in discriminating more subtle malfunctions of the gland than simple overactivity or underactivity. Of course, many other factors such as time and expense will contribute to the selection of a specific diagnostic test, and the second criterion should not be followed too dogmatically. Every effort should be made, however, to express the results of any test in terms of fundamental parameters or, if necessary, to obtain auxiliary information to correlate the test with the fundamental parameters.

Any mathematical formulation must be based on assumptions as to the processes involved in the phenomenon under consideration. The validity of the formulation can be determined only by comparison with experimental results. The process is not then complete because the experiments may indicate further refinements of the mathematical formulation and a resultant increase in the knowledge of the fundamental processes. In the case of thyroid physiology, there is available a relatively large mass of data on the utilization of iodine and radioiodine by the thyroid gland. Keating *et al.* (1) and Astwood and Stanley (2) have analyzed the iodide metabolism of patients, and Oddie (3) has presented an excellent mathematical analysis of thyroid function. However, the comparison of experimental results with a mathematical formulation remains one of the most difficult operations of the general process of analysis, particularly if the comparison is to be made on a routine basis. In this regard, many mathematical and graphical techniques may be applied to simplify the comparison.

Fortunately, from a mathematical point of view, the phenomena involved in the thyroid may be divided into two groups on the basis of widely different time scales. The accumulation of iodide and synthesis of hormone occur in a matter of hours, whereas the release of organic iodine from the thyroid requires days. This allows the two sets of phenomena to be treated

independently, and, if necessary, the interaction of one on the other to be treated as a correction.

IODIDE METABOLISM

The radioiodine is usually administered in the form of an iodide which rapidly diffuses throughout the plasma volume. This volume is represented by the compartment V_1 in Figure 1, which represents a model of the assumed metabolism of iodide. The radioiodide diffuses into a second volume,

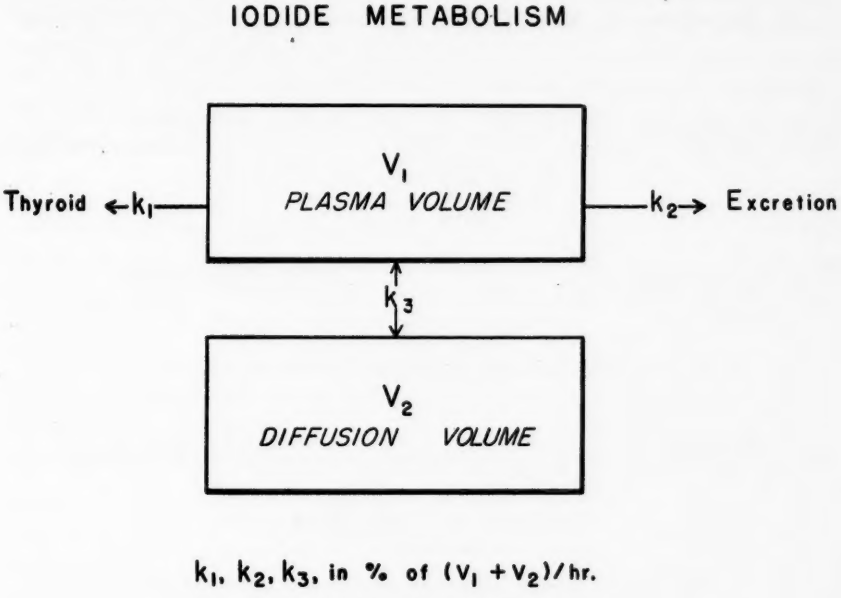

FIG. 1. Model of iodide metabolism.

V_2, with a rate constant k_3. Actually, this is an oversimplification, since there are undoubtedly several diffusion volumes, each with its own rate constant. It is perhaps fortuitous that a single constant gives adequate agreement with experimental results in many cases. The diffusion volume, V_2, consists of the extracellular volume and other iodide-containing body fluids. However, the magnitude of this volume is not defined as a physical volume, but as a volume of fluid of the same iodide content as the plasma and containing the total amount of iodide present in the extra-plasma fluids. This artifice is a convenient alternative to presenting the radioiodide content as a specific activity, or amount of radioiodide per unit amount of iodide. The advantage of this definition is that the concentra-

tion of iodide in the volume V_2 approaches that of V_1 after equilibrium has been reached, and after this time, (V_1+V_2) can be considered as a single volume, usually referred to as the iodide space.

The radioiodide is cleared from the plasma by the thyroid and kidneys with the rate constants k_1 and k_2 respectively. These clearances are non-reversible as compared to the diffusion of radioiodide between the plasma and diffusion volumes.

The variation of radioiodide content of the plasma, the excretion, and the thyroid accumulation are represented in Figure 2. The rate constant k_3 and the volumes V_1 and (V_1+V_2) can be obtained from the semi-log-

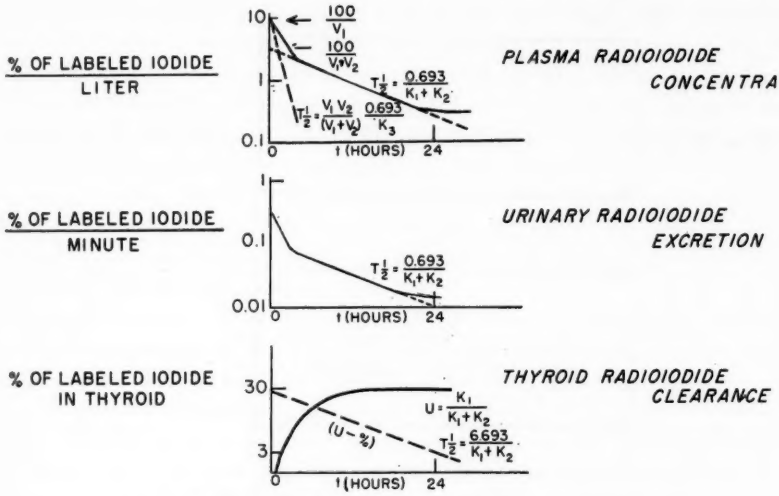

FIG. 2. Radioiodide concentration of plasma, excretion, and thyroid accumulation, on basis of model.

arithmic plasma radioiodide plot as illustrated. The value of (V_1+V_2) is found by extrapolating the second exponential portion of the curve to zero time, and the value of V_1 is found by extrapolating the first exponential curve to zero time. Figure 2 also illustrates how the constant k_1+k_2 may be obtained from either of the three curves—in the first two by measuring the slope or half-period of the second exponential portion of the plots, and in the third curve by measuring the half-period of the exponential curve obtained by subtracting from the total thyroid radioiodide accumulation, U, the thyroid content at the time t. In all three cases, the most convenient datum to obtain directly from the curve is the half period, $T\frac{1}{2}$, or the time necessary for the plasma radioiodide concentration to drop

to one-half its original value. The constant (k_1+k_2) is found by the relation:

$$k_1 + k_2 = \frac{0.693}{T_{\frac{1}{2}}}.$$

The length of time over which the iodide analysis can be made is limited by the appearance of labeled organic iodine in the plasma. If necessary, the organically bound radioiodine may be removed from the sample of plasma or urine and the iodide analysis continued somewhat longer.

To obtain k_1 or k_2 separately, an independent observation must be made. The quantity k_2 (V_1+V_2), may be obtained by dividing the value of excretion found in Figure 2 by the plasma concentration at that time. If (V_1+V_2) is known, the constants k_2 and k_1 may be found. Alternatively, the iodide uptake, U, may be used to find k_1 by means of the following relation:

$$U = \frac{k_1}{k_1 + k_2}.$$

Thus, two independent methods are available for the determination of k_1 and k_2.

HORMONE RELEASE

The assumed fate of labeled hormone released by the thyroid is illustrated in Figure 3. The hormone released from the gland enters the pool of organically bound iodine in the plasma, V_o, is partially excreted in the bound form and partially reduced to iodide by the peripheral tissues. The

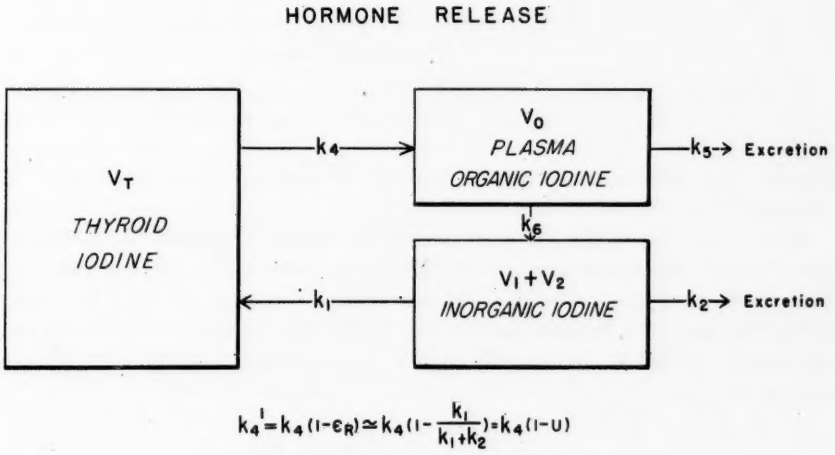

FIG. 3. Model of hormone release.

iodide is then cleared in the same manner as the administered radioiodide. This representation is undoubtedly a simplification, as the hormone must pass through several stages in its formation and degradation. However, a more refined model will have to be based on more complete experimental information than is presently available. The volumes V_t and V_o represent quantities of stable iodine in the same manner as the volume V_2 of the iodide space. Although there is adequate evidence to confirm the excretion of organic iodine in considerable quantities, the rate of excretion, k_5, is

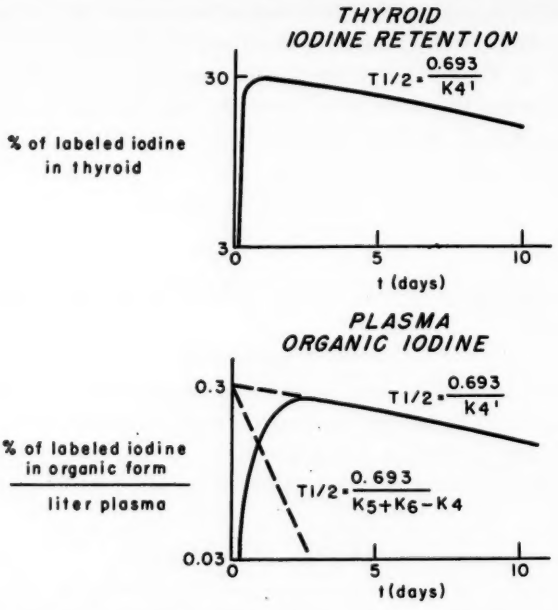

FIG. 4. Radioiodine retention of thyroid and concentration of organic radioiodine in plasma, on the basis of the hormone release model.

known only qualitatively and is one of the most difficult constants to measure.

Figure 4 shows typical curves for the retention of labeled hormone by the thyroid and concentration of labeled organic iodine in the plasma. From both of these curves, the effective release constant, k_4', may be readily determined. The release constant k_4' is less than k_4 as a result of the re-utilization of iodide resulting from the hormone and is given by the following equation:

$$k_4' = k_4(1 - \epsilon_R)$$

where ϵ_R is the re-utilization constant and is the fraction of bound iodine

released by the gland which re-enters as iodide. It is interesting to note that if k_5 were zero, ϵ_R would be:

$$\epsilon_R = \frac{k_1}{k_1 + k_2} = U$$

or the re-utilization constant would be equal to the fractional uptake of iodide. Actually this constant is somewhat less than the uptake, but the relation gives a useful indication of its magnitude.

The concentration of organic radioiodine in the plasma on the basis of the model is represented by the following equation:

$$C_0 = \frac{k_4 U}{(k_5 + k_6 - k_4')V_0} e^{-k_4' t}(1 - e^{-(k_5+k_6-k_4)t}).$$

If k_5 and k_6 are considerably less than k_4', the value of the quantity, $(k_5+k_6-k_4)$, can be obtained graphically, as illustrated in Figure 4. The

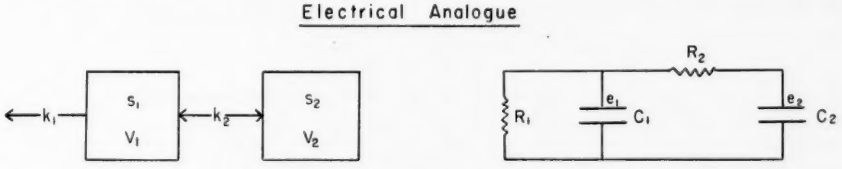

FIG. 5. Biologic and electrical analogue.

plasma concentration is subtracted from the extrapolated curve of slope k_4', and the resultant exponential curve has the slope, $(k_5+k_6-k_4)$. As k_4 is also small, this is approximately the value of (k_5+k_6).

Whereas k_4 is the rate at which the gland releases hormone, k_6 is the rate at which the organic iodine is being utilized and would seem to be characteristic only of the hormone. It would be most advantageous to determine both k_4 and k_6 because of the different aspects of the release of hormone which they measure. The rate constants k_4 and (k_5+k_6) should not be confused with the absolute rate of release and of degradation, $k_4 V_t$ and $(k_5+k_6)V_0$ respectively. The absolute rate of release and of degradation must, of course, be equal if the system is in equilibrium.

COMPUTATION AIDS

The graphic methods presented in the preceding two sections are usually sufficient to obtain satisfactory values of the constants from the experimental data. In many instances, however, and particularly in research studies, it may be desired to analyze more complex models. Analysis by formal mathematical means becomes increasingly difficult as the complexity increases, particularly if even a few subjects are to be studied.

A possible method of analysis is by means of an electrical analogue, a technique which has been found useful in many other fields. Figure 5 illustrates the operation of the analogue device. A simple biologic system consists of two volumes, V_1 and V_2, between which a diffusion path, k_2, exists. One of the volumes, V_1, is cleared at the rate, k_1. The electrical analogue consists of two condensers, C_1 and C_2, and two resistors R_1 and R_2. The analogy becomes apparent when the differential equations for specific activity, s, in the first case and voltage, e, in the second case are compared. For the biologic model:

$$V_1 \frac{dS_1}{dt} = - k_1 V_1 S_1 - k_2 V_1 (S_1 - S_2)$$

$$V_2 \frac{dS_2}{dt} = k_2 V_1 (S_1 - S_2)$$

and for the electrical model:

$$C_1 \frac{de_1}{dt} = - \frac{1}{R_1} e_1 - \frac{1}{R_2} (e_1 - e_2)$$

$$C_2 \frac{de_2}{dt} = - \frac{1}{R_2} (e_1 - e_2).$$

The analogous components are:

$$V \sim C$$

$$kV \sim \frac{1}{R}$$

$$s \sim e$$

and by use of appropriate scaling factors the electrical data can be quantitatively translated into biologic terms. Thus, a radioactive tracer experiment would be analogous to the introduction of a quantity of charge onto one of the condensers. The transient voltage would represent the variation with time of the specific activity of the analogous biologic compartment. In any specific application, the electrical analogue would be constructed from the assumed biologic model, and the constants would be adjusted until the results agreed with the biologic data. The values of the electrical constants would then give the biologic rates and volumes.

DISCUSSION

The constants which would appear to be of primary importance in the study of thyroid physiology are presented in Table 1. Both the thyroid clearance rate, k_1, and the uptake, U, have been presented, as there is

TABLE 1. FUNDAMENTAL PARAMETERS

Constant	Function	How measured
k_1	Thyroid clearance rate	Radioiodide measurement of plasma or excretion. *In vivo* thyroid measurement.
U	Thyroid iodide uptake	*In vivo* thyroid measurement or excretion measurement.
k_4	Hormone release rate	*In vivo* thyroid measurement.
k_6	Peripheral utilization rate	Organic radioiodine measurement of plasma.
(V_1+V_2)	Iodide space	Radioiodide measurement of plasma
V_t	Equivalent thyroid volume	By relation: $k_4V_t=k_1(V_1+V_2)$
V_o	Equivalent organic iodine volume	By relation: $(k_5+k_6)V_o=k_1(V_1+V_2)$

some basis for the opinion that the uptake is the more fundamental constant. For instance, Keating *et al.* (4) have shown that an abnormal renal clearance rate, k_2, produces a thyroid clearance rate such that the iodide uptake remains normal. The renal clearance rate may be desired in some patients, but not primarily in conjunction with the thyroid study. The hormone release rate, k_4, and the peripheral utilization rate, k_6, would appear to be most fruitful in the study of the more specific actions of the thyroid and hormone.

Typical values of the rate constants and volumes for a normal person

TABLE 2. APPROXIMATE VALUES OF CONSTANTS

	Rate constants		Volumes	
	Rate (%/hr.)	Half-period (hrs.)		Volume (liters)
k_1	3	23	V_1	7
k_2	7	10	V_2	18
k_3	750	0.25	V_t	500
k_4	0.15	460	V_o	50
k_5	0.5	140		
k_6	1	70		

are presented in Table 2. The half-periods are those that would be observed if only one rate constant were effective, and are helpful in determining at what time the various constants will be effective. The constants for iodide clearance are based primarily on the date of Keating *et al.* (4) and of Myant, Pochin, and Goldie (5). The constant k_4 appears to vary widely among normal patients, whereas the values of k_5, k_6, V_t, and V_o can be considered only as estimates.

Example

As an illustration of the calculations involved in the iodide metabolism, data on a myxedematous patient are presented in Figure 6. The exponential curves of plasma concentration and urinary excretion are particularly apparent in this case because of the relatively long period of time before organic radioiodine is observed. The constant (k_1+k_2) estimated from the

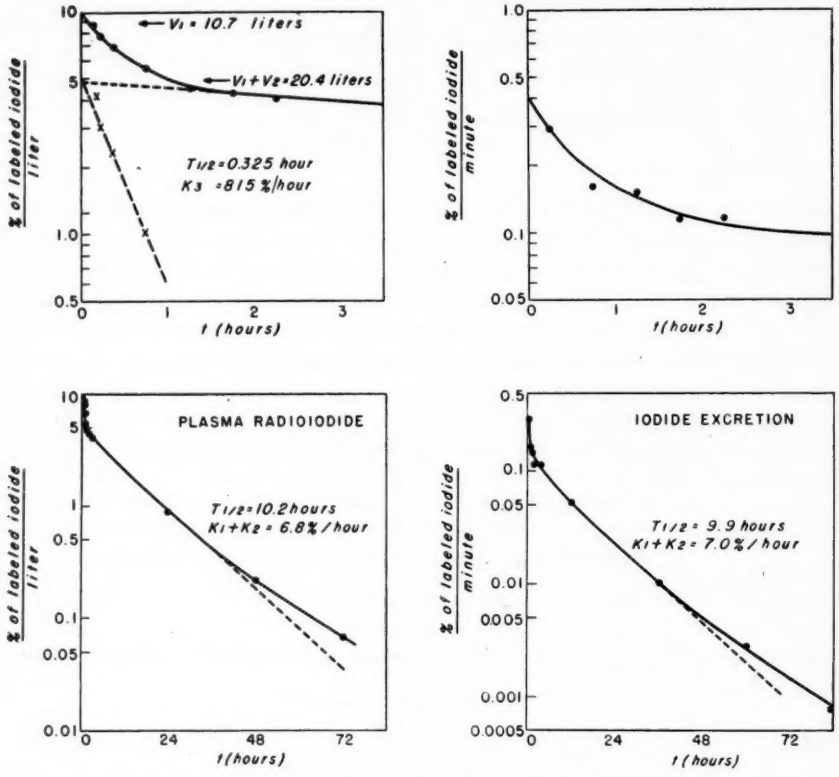

FIG. 6. Radioiodide concentration of plasma and excretion in a myxedematous patient (M. O'M).

plasma concentration is 6.8 per cent per hour, whereas that from the urinary excretion is 7.0 per cent per hour. The ratio of the two curves combined with the value, (V_1+V_2), of 20.4 liters gives a renal clearance rate of 7.2 per cent per hour, indicating that the thyroid clearance rate was virtually zero. This rate was confirmed by an observed four-day iodide excretion of 98 per cent and a 48-hour thyroid uptake of 4 per cent.

Data based on the release of labeled hormone have been presented in an accompanying paper (6) and examples of this phase of thyroid physiology will not be presented here.

SUMMARY

Two criteria are postulated as essential for a radioiodine diagnostic test. The test should be indicative of thyroid status, and the test should measure a fundamental parameter of the thyroid. In support of the second criterion, the metabolism of labeled iodide and the release of labeled hormone by the gland are analyzed on the basis of simple models, and techniques are discussed for the determination of fundamental constants for the experimental data. The metabolism of iodide by a myxedematous subject is presented as an example.

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THE EFFECT OF THYROID-STIMULATING HORMONE IN ACUTE THYROIDITIS*†

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ACUTE thyroiditis, also referred to as acute diffuse thyroiditis, acute nonsuppurative thyroiditis, and subacute thyroiditis, is an inflammatory disease characterized by fever, malaise, and a firm and very tender enlargement of the thyroid gland. The etiology is unknown. Recent studies (1, 2, 3) have disclosed that acute thyroiditis is accompanied by a striking decrease in the ability of the thyroid to concentrate radioiodine after a tracer dose, and by a high normal or slightly elevated serum protein-bound iodine (PBI). Although the diagnosis of this disease is usually clear-cut on clinical grounds alone, the uptake of radioiodine by the thyroid and the serum PBI may be of value in differentiating acute thyroiditis from hemorrhage into an adenoma of the thyroid or from a neoplasm of the thyroid.

Other situations in which a greatly depressed uptake of radioiodine and a normal or elevated serum PBI may coexist are those following the administration of iodine or iodine-containing substances, such as desiccated thyroid and organic iodine-containing dyes used in radiography. In one such patient, a man with thyrotoxicosis factitia, we recently studied the effect of thyroid-stimulating hormone (TSH) on the uptake of radio-

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iodine. Under the influence of TSH, the uptake by the thyroid rose from less than 2 per cent of a tracer dose of radioiodine to 65 per cent. Similarly, Stanley and Astwood (4) have demonstrated an increase in the uptake gradient of radioiodine after TSH administration to patients whose thyroid function was depressed by the administration of desiccated thyroid. In the light of these observations, it became of interest to study the effect of TSH on the depressed uptake of radioiodine in acute thyroiditis.

MATERIALS AND METHODS

Nine patients with acute thyroiditis have been studied. Six of these were observed before and after the administration of TSH.

Radioactive iodine studies were obtained after the oral administration of I^{131} as iodide in doses of 40 to 500 microcuries, containing from 0 to 10 micrograms of stable iodine. Measurements were made of the total radioiodine excreted in the urine in twenty-four and forty-eight hours after the dose. Urinary radioactivity was measured with a gamma-ray counter, compared with an aliquot of the administered dose, and expressed in terms of per cent of the dose. *In vivo* counting was done with an end-window Geiger-Mueller tube, heavily shielded and positioned 22 centimeters from the suprasternal notch (5).

Serum PBI was determined by a modification of the method of Barker (6, 7).

TSH[1] was administered intramuscularly once each day in 20-mg. to 30-mg. amounts except in one patient, (A.W.), who received 15 mg. twice each day. The injections were given for from one to five days. Discomfort at the site of the injection occurred in most patients, and abdominal distress (nausea and, occasionally, vomiting) in some.

The TSH was started at from two to five days after the first tracer dose of radioiodine. The second dose of radioiodine was given two days after the last dose of TSH.

Radioactivity persisting in the thyroid and urine prior to the second dose of radioiodine was so low that correction for this factor was unnecessary.

DESCRIPTION OF PATIENTS AND LABORATORY FINDINGS

Although there was a considerable variation in this group of patients with regard to duration and severity of the illness, most of the clinical features were remarkably similar. In Table 1 are listed the major signs

[1] The TSH was supplied by Armour and Company, Chicago, Ill., through the courtesy of Dr. John R. Mote. Two patients (A.W. and M.M.) received TSH labelled "Armour, 1SR4." Three patients (R.A., M.F., and L.F.) received TSH labelled "Armour, J-13903-R." One patient (J.P.) received TSH labelled "Armour, K-23101."

TABLE 1. MAJOR SIGNS AND SYMPTOMS IN ACUTE THYROIDITIS
Total number of patients—9

	Number of patients
Pain in thyroid area	9
Tenderness in thyroid area	9
Dysphagia	4
Enlargement of thyroid	9
Fever	9
Chills or sweats	5
Malaise	9
Previous respiratory infection	3
Unequivocal hyperthyroidism	0

and symptoms. All of the patients complained of pain and tenderness in the thyroid area, and 4 also complained of dysphagia. In most patients the discomfort was more severe on one side of the neck, and in a few, the first side became painless before the second side was involved. In all patients, however, the entire thyroid gland was enlarged when examined by us. The gland was very firm, usually somewhat irregular, and enlarged, usually asymmetrically, to about two or three times normal size. Tenderness was confined to the limits of the palpable thyroid. A few patients also had a small number of tender pretracheal lymph nodes. None of the patients was known to have had pre-existing thyroid disease.

All patients had fever, which varied from low grade elevations of about 100° F. to spiking temperature courses as high as 105° F. Profuse sweats

TABLE 2. SUMMARY OF CLINICAL AND LABORATORY DATA IN ACUTE THYROIDITIS

Pt.	Sex	Age (yrs.)	Duration of illness before examination (weeks)	Severity* of illness	Maximum temp. (°F)	Maximum total WBC (cells/cu. mm.)	BMR (% of normal)	Serum cholesterol (mg./100 cc.)	Serum PBI (micrograms per 100 cc.)
R.A.	M	29	4	Moderate	100.4	7,800	− 5	159	—†
M.F.	M	42	1	Severe	105	11,000	+11	129	—†
A.W.	F	39	2	Moderate	101	6,800	−14	229	8.6
M.M.	F	50	5½	Severe	104	12,800	−13	217	9.4
L.F.	F	49	13	Severe	102.8	12,500	− 8, − 6	239, 266	8.3
J.P.	M	43	3	Moderate	103	13,800	+26	134	6.2
J.K.	F	49	5	Mild	—†	10,000	+41, +26	237	—†
L.T.	F	50	6	Severe	104.5	7,500	+ 5, − 5	148, 167	6.2
E.R.	F	42	8	Mild	100	10,600	− 1	223	—†

* Classified as mild, moderate or severe with regard to signs and symptoms.
† Not measured.

and mild chills accompanied the higher fevers. All patients complained of malaise, which was often severe. Three patients had upper respiratory infections shortly before the onset of thyroiditis. No patient had had known contact with anyone ill with thyroiditis.

None of the patients was judged clinically to be hyperthyroid, although evidences of mild hyperthyroidism could not be well evaluated in the presence of a febrile illness.

Other findings in these patients are recorded in Table 2, and agree in most particulars with those reported in the literature (8). Two-thirds of the patients were women. The age varied from 29 to 50 years with an average of 43.7 years. The total white blood count was elevated in 4 patients, never higher than 13,800; in the others, the white blood count was normal.

TABLE 3. RADIOIODINE TRACER STUDIES IN ACUTE THYROIDITIS BEFORE AND AFTER TSH

Pt.	Duration of illness before tracer (weeks)	TSH dose (mg./day × no. of days)	Thyroid I^{131} uptake at 48 hours (% of dose)		Urinary I^{131} excretion (% of dose)			
					Before TSH		After TSH	
			Before TSH	After TSH	24 hrs.	48 hrs.	24 hrs.	48 hrs.
R.A.	5½	30×5	<2.0	14.9	71.2	75.6	56.8	69.8
M.F.	1½	30×5	0.8	6.7	79.1	100.0	73.3	85.6
A.W.	2½	30×3	2.3	37.1	50.3	—†	43.1	46.4
M.M.	6	30×3	0.4	6.2	78.0	89.0	67.2	77.4
L.F.	13½	30×2 20×1	2.1	36.6	72.6	82.0	54.0	56.6
J.P.	3	25×1	0.5	9.6	80.0	84.8	81.6	88.0
J.K.	5*	—	0.3	—	60.0	67.2	—	—
L.T.	7	—	0.1	—	81.5	90.6	—	—
E.R.	8**	—	18.8	—	61.0	69.6	—	—

* Asymptomatic for at least one week prior to tracer study.
** Recovering from illness at time of tracer study.
† Not measured.

The differential white count revealed a slight elevation of lymphocytes (up to 35 per cent) in 6 patients, but was otherwise normal. The erythrocyte sedimentation rate when measured was uniformly elevated, ranging from 30 to 50 millimeters per hour.

The results of the thyroid function tests are also recorded in Table 2. The BMR was elevated in 2 patients and normal in the others. The serum cholesterol was below normal in 3 patients and normal in the others. The serum PBI was measured in 5 patients; it was found to be normal in 2 and slightly elevated in 3, and ranged from 6.2 to 9.4 micrograms per 100 cc.[2]

The results of the radioiodine tracer studies are recorded in Table 3. A striking decrease in the uptake of radioiodine by the thyroid was noted

[2] The normal range for serum PBI in our laboratory is 4 to 8 micrograms per 100 cc.

in all but 1 patient. In 8 of the 9 patients studied, the uptake at forty-eight hours, was 2.3 per cent of the dose or less. One patient (E.R.), who was recovering from her illness at the time of the study, concentrated 18.8 per cent of the dose in her thyroid. Another patient (J.K.), however, had been asymptomatic for at least a week before her tracer study, at which time the uptake by the thyroid was only 0.3 per cent.

The urinary excretion of radioiodine in forty-eight hours was greater than 82 per cent in 5 cases, and over 67 per cent in all cases. In 1 patient (A.W.), the data on urinary excretion were incomplete.

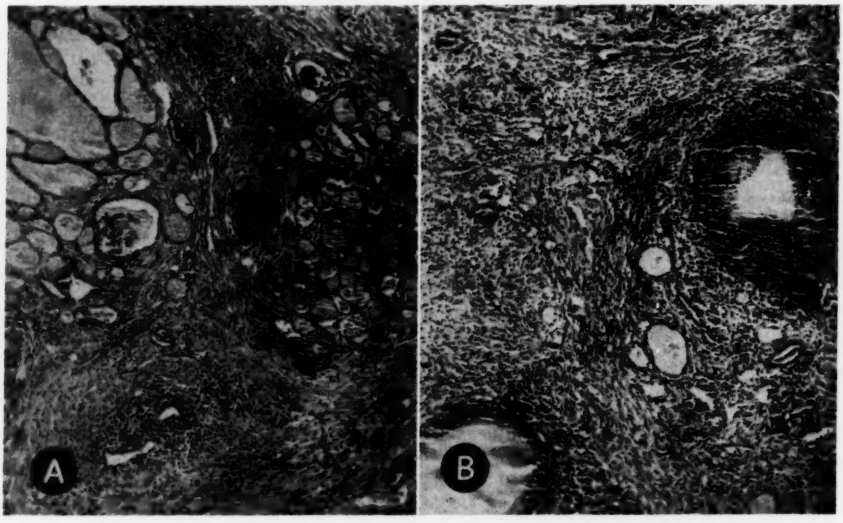

FIG. 1. A and B. Histologic sections from biopsy specimen of the thyroid isthmus in a patient (J.P.) with acute thyroiditis. ×80.

In 2 patients (E.R. and J.P.) surgical biopsy specimens of the thyroid were taken. Microscopic sections of one (from J.P.) are shown in Figure 1. In both glands there was a diffuse inflammatory reaction with mononuclear cell infiltration predominating, a moderate fibrous tissue proliferation, and giant cell formation. An occasional microscopic abscess was seen in both specimens, but there was no gross suppuration.

EFFECT OF THYROID-STIMULATING HORMONE

The effect of TSH on the uptake of radioiodine by the thyroid and on the urinary excretion of radioiodine is summarized in Table 3. It may be seen that TSH brought about an increase in the ability of the thyroid gland to concentrate iodine. From a pretreatment level ranging from 0.4

to 2.3 per cent of the administered dose, the uptake by the thyroid at forty-eight hours rose to a level ranging from 6.2 to 37.1 per cent. This change is illustrated graphically in Figure 2. It should be noted, however, that the uptake rose to a normal value in only 2 patients, and in none did it rise to a level higher than normal. This is to be compared with the effect of TSH on our patient with thyrotoxicosis factitia, on euthyroid subjects

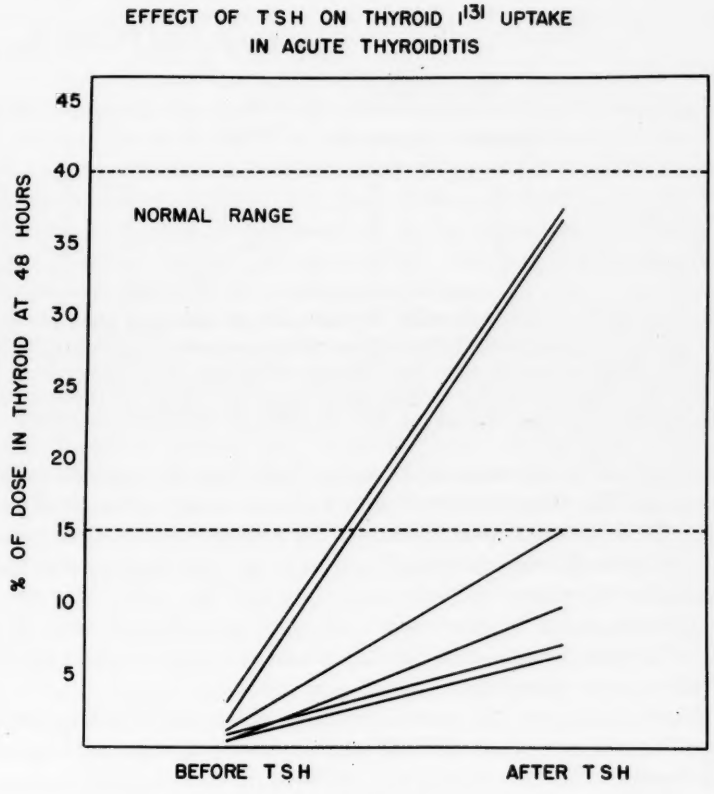

FIGURE 2.

(9), and on a patient with pituitary myxedema (10), in whom the uptake by the thyroid rose considerably above normal.

The increase in uptake of radioiodine was generally reflected in a fall in urinary excretion of radioiodine, as may be seen in Table 3. The response to TSH apparently bore no relation to the duration of the thyroiditis or to the amount of TSH administered.

In 2 patients, the serum PBI was measured before and after TSH. In

one (M.M.) the PBI rose from 9.4 to 11.8 micrograms per 100 cc. In the other (J.P.), no change in the PBI occurred.

It was also observed that the administration of TSH was followed by a marked effect on the clinical manifestations of these patients. The results are indicated in Table 4, and are compared with the response of these patients to other forms of treatment. Of the 6 patients who received TSH, 4 had definite improvement in their clinical status, 1 had equivocal improvement, and 1 appeared to be worse following the administration of the hormone. The improvement began within two days after the first dose of TSH. Of those who were improved, all experienced relief of pain and tenderness over the thyroid gland, and in 3 patients these symptoms disappeared. In 3 patients the fever also subsided, but in 2, fever persisted despite symptomatic improvement. All but 1 experienced relief of their malaise. No definite change in the size or texture of the thyroid gland was observed to accompany the symptomatic changes.

TABLE 4. EFFECT OF TSH ON CLINICAL STATUS IN ACUTE THYROIDITIS

Therapy*	Improvement		No change	Worse	Total
	Definite	Equivocal			
TSH	4	1	0	1	6
Propylthiouracil	1	2	0	0	3
X-ray	0	2	0	1	3
Antibiotic	0	0	6	0	6

* See text for description of results. Several patients had more than one form of therapy during the course of their illness. Four of the 5 patients improved by TSH later had relapses. Propylthiouracil doses were 300 mg. to 600 mg. daily for twelve to seventeen days. The total dose of x-ray therapy varied from 500 to 600 r. Antibiotics included aureomycin, chloromycetin, terramycin and penicillin in various combinations.

With one exception, the only treatment which these patients received prior to the administration of TSH was antibiotic therapy with aureomycin, chloromycetin, terramycin or penicillin in various combinations. In no instance did the clinical course appear to be affected by such antibiotic therapy. One patient, who experienced equivocal improvement after receiving TSH, had received x-ray therapy three weeks prior to the administration of TSH.

Calculation of the approximate roentgens-equivalent-physical (r.e.p.) of beta radiation delivered to the thyroid by the tracer dose of radioiodine in these patients (11) revealed a maximum of 5 r.e.p. after the pre-TSH tracer and a range of 15 to 150 r.e.p. following the post-TSH tracer. With regard to the possible contribution of the larger amounts of irradiation to

the clinical changes observed in the patients, it should be noted that the symptomatic improvement preceded the second dose of radioiodine.

Of the 5 patients who experienced improvement after the administration of TSH, 4 had a relapse of the thyroiditis within one to seven days after the last injection of the hormone. In 2 of these, only the fever recurred. In 1, pain and tenderness in the thyroid recurred as well as fever. In 1, only pain and tenderness recurred. In 3 patients, the relapse was mild and was followed by a rapid recovery without further treatment. One patient returned to his pretreatment status.

The consistency and abruptness of the clinical changes following TSH support the belief that these were causally related. In the patients treated with propylthiouracil and x-ray there was a suggestion of improvement but the change, except in 1 patient after propylthiouracil, was so gradual as to be indistinguishable from that which might occur in the natural course of this disease. There are data in the literature, however, which indicate that the clinical course of acute thyroiditis may be favorably influenced by thiouracil (12) and x-ray therapy (8).

The striking decrease in the ability of the thyroid gland to concentrate iodine during the active phase of acute thyroiditis has again been demonstrated, but the mechanism of this change remains obscure. Presumably, it is due to a uniform damage of the acinar cells by the inflammatory process. Another explanation, particularly in view of the occasionally elevated PBI and the absence of hypothyroidism in these patients even after a prolonged illness, is that the damaged thyroid follicles release an excessive amount of thyroid hormone into the circulation, which in turn, brings about depression of thyroid function either directly or via the pituitary. It is also possible that the infection itself may interfere with thyroid function by depressing pituitary activity. The latter hypothesis would explain the effectiveness of injected TSH in increasing thyroid function in these cases. This does not, however, explain the effects of TSH on the clinical status of the patient, and it may be that TSH in some way affects the inflammatory process itself.

Follow-up of patients

The eventual outcome in the patients studied was improvement, regardless of the therapy employed. The over-all duration of illness, with respect to signs and symptoms of inflammation, varied from three and one-half to sixteen and one-half weeks. The decrease in size and hardness of the gland itself was a slower process. Four patients still had firm, enlarged thyroid glands, although with evident improvement, at from three to ten months after the onset of illness, or from one-half to eight months after disappearance of other evidences of illness. Two patients (M.F. and

L.F.) had normal sized or nonpalpable glands at four, and six and one-half months respectively, after the onset of illness, or two and one-half months after they became well.

Three patients were given tracer doses of radioiodine at from four to ten and one-half months after the onset of illness. Two (M.F. and L.F.) had normal uptakes of radioiodine by the thyroid. One (J.K.), a patient who had received no treatment of any kind, had a slightly elevated uptake of 44.4 per cent. In 1 patient (J.P.), the uptake by the thyroid was 0.6 per cent two weeks after the dose of TSH. This may be an indication that the effect of TSH on thyroid uptake of radioiodine was transient, but may also be due to the post-stimulation refractoriness of the thyroid which may follow TSH administration (9).

In none of the patients in this study has the development of hypothyroidism been observed, in contrast to the findings of Keating *et al.* (3) who reported the development of myxedema in 4 of 16 patients with acute thyroiditis.

SUMMARY

Nine patients with acute thyroiditis have been studied and their clinical and laboratory findings reviewed. Eight of these patients had a marked decrease in thyroid function as evidenced by an uptake of radioiodine by the thyroid of 2.3 per cent of the dose or less at forty-eight hours. The serum PBI when measured was normal or slightly elevated. All patients were clinically euthyroid.

Six patients were treated with thyroid-stimulating hormone in doses of 25 to 150 mg. intramuscularly over a one-day to five-day period. TSH induced an increase in the uptake of radioiodine by the thyroid in all instances, but in only 2 patients did this reach normal levels. In 5, improvement in clinical signs and symptoms was also observed, but in 4 of these patients the disease had relapsed within a week after treatment.

All patients ultimately recovered from their illness, regardless of treatment, but resolution of the thyroid enlargement was a slow process. This small series allows no conclusions as to effective means of hastening recovery.

Acknowledgment

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RADIOIODINE STUDIES IN THYROIDITIS*

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DESPITE considerable literature on the pathology of acute and chronic thyroiditis, comparatively little is known about the functional status of the thyroid in these conditions. Recently radioiodine tracer technic has provided a means of observing some aspects of thyroid function in thyroiditis. It is the purpose of this paper to present the results of radioiodine tracer studies performed on 40 patients, of whom 21 had acute diffuse thyroiditis, 13 had struma lymphomatosa and 6 had struma fibrosa.

TABLE 1. SUMMARY OF THE RADIOIODINE VALUES FOR THE THREE CONDITIONS STUDIED AND FOR NORMAL SUBJECTS

Condition	No. of cases	24-Hour thyroidal accumulation, per cent of dose		No. of cases	48-Hour urinary excretion, per cent of dose		Extrarenal disposal rate, per cent per hour		Renal excretion rate, per cent per hour	
		Range	Mean		Range	Mean	Range	Mean	Range	Mean
Acute diffuse thyroiditis	13	0 –18.3	3.0±1.5*	21	64.3–93.4	83.7±2.3	0.2–3.9	1.4±0.2	3.5–13.2	8.0±0.5
Struma lymphomatosa	9	0 –36.7	18.5±4.5	13	38.8–84.9	62.8±3.9	1.1–6.7	4.1±0.7	2.9– 7.7	6.2±0.5
Struma fibrosa	3†	11.0–23.9	18.1±3.8	6	47.3–91.1	75.9±6.8	0.8–2.4	1.8±0.3	2.7– 9.6	7.1±1.0
Normal subjects‡	98	6.0–45.0	24.7±1.2	157	450.–82.0	63.5±0.8	1.3–7.6	3.9±0.1	4.0–10.0	6.7±0.2

* The value following the ± is the standard error of the mean.

† In 2 of these 3 cases the thyroidal accumulation was measured only at forty-eight hours.

‡ Reported by Keating and associates (5).

MATERIAL AND METHODS

Tracers consisting of 100 or 300 microcuries of I^{131} with 100 micrograms of sodium iodide added as carrier were administered by mouth to the subjects in the fasting state. After the ingestion of the I^{131}, *in vivo* counts were taken over the thyroid at twenty-four or forty-eight hours as described by Luellen and associates (1), and urinary excretion of I^{131} was evaluated

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as described by Keating and associates (2). From the curve of urinary excretion, two rates were estimated: 1) the renal excretion rate, defined as the proportional rate at which inorganic radioiodide is being removed from the blood by the kidneys, and 2) the extrarenal disposal rate, defined as the proportional rate at which radioiodide is being removed from the blood by all tissues other than the kidneys. The values for these rates in our patients with thyroiditis are compared with the values in euthyroid persons reported elsewhere (Table 1).

TABLE 2. LEVELS OF THE BASAL METABOLIC RATE IN PATIENTS WITH THYROIDITIS

Basal metabolic rate, per cent	Number of cases*		
	Acute diffuse thyroiditis	Struma lymphomatosa	Struma fibrosa
−29 to −20	0	3	1
−19 to −10	1	3	1
− 9 to 0	4	4	1
+ 1 to +10	7	2	1
+11 to +20	6	0	1
+21 to +30	2	0	0
Mean basal metabolic rate, per cent	+7.1±2.5†	−9.8±2.7	−4.4±6.2

* In 1 case in each of the three disease groups the basal metabolic rate was not determined.

† The value following the ± is the standard error of the mean.

RESULTS

Acute diffuse thyroiditis.—Acute diffuse thyroiditis is here defined as an acute or subacute illness characterized by an enlarged, firm, exquisitely tender thyroid, a very high erythrocyte sedimentation rate and, frequently, marked systemic symptoms including fever, chills, tachycardia, loss of weight and night sweats. The microscopic appearance of the thyroid includes degeneration of epithelial cells, decrease of colloid, infiltration with polymorphonuclear leukocytes and small round cells, fibrosis, and foreign body reaction.

In acute diffuse thyroiditis the basal metabolic rate is often greater than normal, and sometimes the patients also have symptoms of hyperthyroidism. The basal metabolic rate was more than +10 per cent in 8 of our cases, the highest reading being +26 per cent. Two patients were thought clinically to be mildly hyperthyroid, and in these 2 the basal metabolic

rates were +19 per cent and +26 per cent. Despite high basal metabolic rates in the other 6 patients, clinical evidences of hyperthyroidism were lacking. The mean basal metabolic rate was $+7.1 \pm 2.5$ per cent (Table 2). In 6 of these patients myxedema subsequently developed, but 12 remained euthyroid following the thyroiditis. In the other 3 instances the ultimate thyroidal state is unknown.

In vivo counts over the thyroid were made twenty-four hours after the ingestion of I^{131} in 13 of the 21 patients. The uptake for the majority of these was significantly less than that of normal persons. Of the 13 patients,

TABLE 3. URINARY EXCRETION OF I^{131} IN FORTY-EIGHT HOURS

Per cent of dose	Number of cases		
	Acute diffuse thyroiditis	Struma lymphomatosa	Struma fibrosa
30–39	0	1	0
40–49	0	2	1
50–59	0	2	0
60–69	1	5	0
70–79	5	2	2
80–89	7	1	2
90–99	8	0	1

uptake was zero or insignificant in 7, between 1 per cent and 5.2 per cent of the dose in 4, 10.6 per cent in 1, and 18.3 per cent in 1. Two other patients, 1 of whom had *in vivo* measurements made at nine hours and 1 at forty-eight hours after the ingestion of radioiodine, also showed low uptakes, 0.4 per cent and 5.8 per cent, respectively. The mean uptake for the 13 patients measured at twenty-four hours was 3.0 ± 1.5 per cent of the dose. Werner and co-workers (3), Crile and Rumsey (4), and Keating and associates (5) have previously reported that the thyroids of patients with acute diffuse thyroiditis collect less radioiodine than do the thyroids of normal persons.

The 48-hour urinary excretion of I^{131} in our 21 patients exceeded the normal range in 13, was in the high normal range in 6, and was close to the mean normal value in only 2. Table 3 shows the distribution of these figures. The mean value for the urinary fraction in these 21 cases was 83.7 ± 2.3 per cent of the dose.

The extrarenal disposal rate (which in all *except* myxedematous persons approximately reflects the proportional rate at which the thyroid collects I^{131} from the blood) was lower than normal in most of the patients with acute diffuse thyroiditis. The range of these values was from 0.2 to 3.9 per cent per hour, with a mean of 1.4 ± 0.2.

The results of the radioiodine studies in the 8 patients who had elevated basal metabolic rates (2 of whom were thought clinically to be hyperthyroid) did not differ significantly from those of the studies in the other 13 with normal rates.

One would expect that renal function in patients with acute diffuse thyroiditis would not be impaired by the disease, and that, therefore, the renal excretion rate would be normal. This was found to be the case. In the 21 patients studied, it varied from 3.5 to 13.2 per cent per hour with a mean of 8.0 ± 0.5.

Struma lymphomatosa.—Struma lymphomatosa is the chronic type of thyroiditis described in 1912 by Hashimoto (6) and characterized by a pathologic picture of diffuse lymphocytic infiltration with numerous lymphoid follicles in which germinal centers are often present.

Although a normal basal metabolic rate is the rule, myxedema is observed fairly frequently in persons with this condition when they are first seen by the examiner. Eventually myxedema develops in most of these patients. Of our 13 patients with struma lymphomatosa,[1] 5 had myxedema when they were first seen, in 4 myxedema developed postoperatively, 2 have not become myxedematous and 2 have had thyroiditis too recently for one to know what their ultimate thyroid status will be. The mean initial basal metabolic rate was -9.8 ± 2.7 per cent (Table 2).

The values of the radioiodine studies were normal in most of the patients with struma lymphomatosa, including all 5 who were thought clinically to have myxedema at the time the tracer was given. *In vivo* counts or analyses of thyroid tissue removed at operation were made on 11 of the 13 patients. In 2 (neither of whom had myxedema) the thyroids collected too little I^{131} to measure, but in the other 9, fairly normal counts were obtained. In 1 patient an *in vivo* analysis showed a thyroidal uptake of 25 per cent of the dose at six and a half hours, in another patient the uptake was 15 per cent at forty-eight hours, and in the remaining patients the uptake ranged from 12 to 37 per cent of the dose at twenty-four hours. The mean uptake in the 9 patients measured at twenty-four hours was 18.5 ± 4.5 per cent of the dose.

Werner and associates (3) found that in 6 of 7 patients with chronic thyroiditis (both Hashimoto's and Riedel's) the thyroidal collection of radioiodine was normal or greater than normal. Dempsey and others (7) reported that in 1 case of struma lymphomatosa the two-hour thyroidal uptake of an I^{131} tracer was less than normal.

The 48-hour urinary excretion of I^{131} in the patients with struma lym-

[1] In all but 1 case the diagnosis was confirmed by examination of pathologic tissue. Since in the thirteenth case no tissue was examined, the diagnosis in this case must be considered as probable struma lymphomatosa.

phomatosa was greater than normal in 1, less than normal in 1, and within the normal range in the other 11. The mean value for the 13 patients was 62.8 ± 3.9 per cent of the dose. Table 3 gives the distribution of these cases.

The extrarenal disposal rate was within the normal range in most of the patients studied, varying from 1.1 to 6.7 per cent per hour, with a mean of 4.1 ± 0.7. The renal excretion rate was essentially normal in all subjects. It varied from 2.9 to 7.7 per cent per hour, with a mean value of 6.2 ± 0.5.

Struma fibrosa.—Struma fibrosa is the chronic type of thyroiditis described in 1896 by Riedel (8) and characterized by a pathologic picture of dense fibrosis with scattered atrophic acini.

Myxedema at the time the patient is first seen has seldom been reported, and in none of our cases was myxedema present initially. The basal metabolic rate varied between -23 per cent and $+13$ per cent with a mean of -4.4 ± 6.2 per cent (Table 2). Postoperative myxedema is said to occur in about one fourth of the patients with Riedel's thyroiditis. Of our 6 patients, all of whom underwent thyroid surgery, in 3 postoperative myxedema is known definitely to have developed, in 1 it probably developed, and in 2 the records are incomplete.

In vivo counts were made on 3 of the patients with Riedel's thyroiditis and in each instance the thyroid uptake was within the normal range. At twenty-four hours in 1 case the uptake was 19 per cent and at forty-eight hours in 2 cases it was 11 and 24 per cent of the dose.

The 48-hour urinary excretion of radioiodine was within the normal range in 4 cases and greater than normal in 2. Table 3 lists the distribution of these values. The mean figure was 75.9 ± 6.8 per cent of the dose.

The extrarenal disposal rate was low in all patients with struma fibrosa, varying between 0.8 and 2.4 per cent per hour, with a mean of 1.8 ± 0.3; but the renal excretion rate was normal, ranging from 2.7 to 9.6 per cent per hour, with a mean of 7.1 ± 1.0.

COMMENT

The foregoing observations indicate that radioiodine tracer studies are of diagnostic usefulness in acute diffuse thyroiditis. In a nonmyxedematous patient suspected of having this disease, low thyroidal uptake and high urinary excretion of a tracer would support such a diagnosis.

The results of I^{131} studies in acute diffuse thyroiditis suggest that this condition interferes with the accumulation of iodine in the thyroid. Since thyroidal iodine accumulation has been shown usually to reflect the process of hormonal biosynthesis, the latter may be presumed to be reduced. However, the liberation of thyroid hormone from the thyroid into the blood stream appears to continue at a normal and sometimes possibly at an accelerated rate during a considerable part of the disease, as can be inferred

from the clinical condition of the patients, the basal metabolic rates and the levels of serum precipitable iodine.[2] It may be that if the disease abates before the hormonal stores in the gland are exhausted, myxedema does not develop. This appears to have been the course of events in 12 of the 21 patients we studied. On the other hand, if hormonal stores in the thyroid are exhausted because of reduced synthesis of the hormone resulting from a long-continued or especially severe inflammation, myxedema may then follow. Myxedema occurred in 6 of the 21 patients.

In most of the patients with struma lymphomatosa and struma fibrosa, the thyroidal uptake and urinary excretion of I^{131} were normal. This was so, even in the 5 patients who, at the time the tracer was given, had associated clinical myxedema. These results are the reverse of those in acute diffuse thyroiditis, but resemble those reported in certain cretins (9, 10) who are profoundly hypothyroid and yet accumulate I^{131} in their thyroids in normal amounts. It has been shown that the I^{131} so accumulated in these cretins is not converted to protein-bound iodine to any significant degree (10). It may be that in like manner the thyroids of patients with chronic thyroiditis do not synthesize a normal amount of thyroid hormone even though they collect iodide normally; direct information as to whether or not this actually is the case, is of course lacking. Nevertheless, it must be concluded that in patients with thyroiditis, whether acute diffuse or chronic, thyroidal accumulation of I^{131} is not a valid measure of hormonal secretion, as it is in most other circumstances.

SUMMARY

Thyroidal accumulation of tracer doses of I^{131} was usually impaired in 21 patients with acute diffuse thyroiditis, although the patients were euthyroid or hyperthyroid. Thyroidal accumulation of I^{131} was usually normal in 19 patients with chronic thyroiditis, although 5 of the patients with struma lymphomatosa had myxedema. The collection of I^{131} by the thyroid in these conditions is not a measure of the secretion of thyroid hormone.

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CLASSIFICATION OF THYROIDITIS, WITH SPECIAL REFERENCE TO THE USE OF NEEDLE BIOPSY*

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DESPITE wide acceptance of the classification of so-called thyroiditis into the three distinct types, namely, subacute thyroiditis, struma fibrosa (Riedel) and struma lymphomatosa (Hashimoto), there still exists some confusion in the recognition of these lesions. The main difficulty seems to lie in the differentiation of subacute thyroiditis from Riedel's struma.

Subacute thyroiditis, struma lymphomatosa, and Riedel's struma are separate entities which do not progress from one to the other. Graham and McCullagh's (1) studies of struma lymphomatosa, those of McClintock and Wright (2), and our own observation of a patient with struma lymphomatosa showing the same histologic picture twenty-three years after the first biopsy indicate that struma lymphomatosa does not progress to Riedel's struma.

Biopsies of the thyroid glands from 14 patients in the clinically acute phase of subacute thyroiditis have shown that this disease is identical histologically with the pathologic entity of pseudotuberculous or giant-cell thyroiditis. Nearly 100 patients with this disease, clinically diagnosed, have been followed until the inflammatory process has subsided and the thyroid is normal to palpation; in no instance has there been any evidence of the irreversible changes characteristic of Riedel's struma.

In the more chronic forms of subacute thyroiditis, the thyroid is often removed surgically, and many pathologists and surgeons classify these glands as Riedel's struma. Since subacute thyroiditis, even in its most chronic form, is a self-limited disease that does not require operation, and since Riedel's struma is an irreversible process from which relief can be obtained only by surgical intervention, it is important to stress once more the differences between the two conditions. These are listed in Table 1.

It is fair to assume that any surgeon who speaks of having removed a Riedel's struma is in reality speaking of a subacute thyroiditis. The in-

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TABLE 1

Riedel's struma	Subacute thyroiditis
Rare	*Common*
Characterized by fibrosis and chronic inflammation.	Characterized by foreign-body giant-cell reaction.
Usually unilateral.	Usually bilateral.
Adenomas usually present.	Adenomas rarely present.
No response to x-ray therapy.	Favorable response to x-ray therapy.
Extensive fibrosis involving all structures around the thyroid.	No extension of inflammation beyond the thyroid.
Impossible to remove the thyroid due to involvement of trachea, carotid sheath and all adjacent structures.	Thyroid easily removed and not particularly adherent.
Preoperative diagnosis—inoperable cancer.	Preoperative diagnosis—thyroiditis or adenomatous goiter.
Irreversible changes.	Self-limited disease, which ultimately resolves.

volvement of the muscles, the carotid sheath, the trachea, the recurrent nerve and the parathyroids in the inflammatory process which embraces all of the structures around the thyroid renders the conventional thyroidectomy impossible to accomplish. All that one can do is to excise a portion of the lobe or isthmus in hope of relieving the symptoms of pressure, or to enucleate the adenoma which usually is found at the center of the mass. X-ray therapy has no beneficial effect on the extensive fibrosis that characterizes this disease.

Since even the most chronic forms of subacute thyroiditis resolve promptly in response to x-ray therapy and since the amount of radiation necessary to induce remission is not sufficient to have any effect on the function of the thyroid, thyroidectomy should be avoided. In the chronic forms of this disease, especially when the involvement is unilateral or one lobe is more prominent than the other so that the possibility of carcinoma must be considered, it is desirable to confirm the diagnosis before x-ray therapy is given.

In subacute thyroiditis the sedimentation rate usually is high and the uptake of radioactive iodine is almost always extremely low. These findings, coupled with a hard diffuse enlargement of both lobes or occasionally only one lobe of the thyroid should suffice to establish the diagnosis, particularly if the gland is tender or if there is a history of pain and fever. But even these findings may be misleading in the exceptional case, and when there is any doubt the matter can be settled by a special method of biopsy. performed with a needle.

The Silverman needle, extensively used by internists for biopsy of the liver, does not obtain material by aspiration but cuts out a core of thyroid tissue in which the architecture is well preserved when obtained. From these biopsies, the pathologist usually can make a definite diagnosis, or can say that the tissue removed is consistent with a certain diagnosis. On rare occasions there may be such distortion of marginal cells that interpretation is not feasible but this has not exceeded 5 per cent in the series we have studied so far. To insure preservation, the fresh tissue specimen should be fixed immediately. Zenker's fluid (potassium dichromate 2.5 per cent, mercuric chloride 4 per cent, in distilled water) has proven most satisfactory since it leads to least tissue distortion. When microradioautographs are desired the tissue fragment is fixed in 10 per cent formalin. The procedure can be performed in the office with no anesthesia except procain infiltrated into the skin, and no noticeable scar is left. We have performed over 100 biopsies of the thyroid with the Silverman needle and have employed it in nearly all types of cases, benign and malignant, with and without hyperthyroidism, and have encountered no bleeding or other immediate complications. The technic of the biopsy has been described elsewhere (3).

The specimens from the glands with subacute thyroiditis have usually been well preserved and suitable for accurate pathologic diagnosis. On a rare occasion it has been impossible to determine whether the inflammation and fibrosis were due to struma fibrosa or to subacute thyroiditis, since it is not always possible to demonstrate a characteristic histiocytic and foreign-body reaction. Struma lymphomatosa can be diagnosed with certainty when small oxyphilic follicles, dense lymphocyte and plasma-cell infiltration and perhaps fibrosis are found, but when the follicles are not so characteristic the lesion is reported as compatible with struma lymphomatosa or exhaustion atrophy. Occasionally the histologic findings are not specific and the diagnosis of fibrosis or thyroiditis of unclassified type must be made. No difficulty has been encountered in differentiating struma from neoplasm.

Although the Silverman needle is of great value in establishing the exact nature of malignant tumors of the thyroid and in obtaining specimens for radioautographs, it should not be employed in cases in which the presence of an operable carcinoma is suspected. Even papillary carcinomas of low-grade malignancy can be implanted in the skin and subcutaneous tissues when a biopsy specimen is removed with a needle, as proven by a case in which the patient refused operation and such a biopsy was followed a year later by transplantation of the tumor to the skin (3).

Struma lymphomatosa may be difficult to diagnose clinically, because the firm bosselations and the tendency for the lobes to differ in size may simulate multinodular goiter. Prior to 1945 at the Cleveland Clinic the

diagnosis of struma lymphomatosa was almost never made before operation. In the past five years we have been able to recognize the majority of cases clinically and have been able to avoid operation in many instances by treatment with x-ray. The Silverman needle has been of great value in establishing the diagnosis.

A firm, bilateral, slightly irregular enlargement of both lobes with preservation of the normal contour of the thyroid, especially when found in a woman in her late forties or fifties, suggests struma lymphomatosa. If, in addition, the basal metabolic rate is below zero or if hypothyroidism is present, there is strong presumptive evidence that the goiter is struma lymphomatosa and a biopsy specimen should be obtained. Patients with multinodular goiters rarely have hypothyroidism and their basal metabolic rates tend to be above zero rather than below.

There is another group of cases in which the entire histologic picture of struma lymphomatosa is not present but which may resemble struma lymphomatosa clinically. This condition, which we call lymphoid thyroiditis, is seen in a younger age group than is struma lymphomatosa, and although there is extensive infiltration with lymphocytes, the typical oxyphilic epithelium is lacking. The usual history is that of a young woman or even of a child noting a rapid diffuse enlargement of a previously normal-appearing thyroid. There are no symptoms, and usually there is no clinical evidence of hypothyroidism. The basal metabolic rate usually is below zero. The thyroid is firm, symmetrical, and may be enlarged to three or four times its normal size.

After the presence of lymphocytic infiltration was confirmed by biopsy with the Silverman needle, several of these patients were treated by x-ray or by administration of desiccated thyroid in doses of 3 grains or more daily, or by a combination of both measures. The goiters disappeared in response to this treatment. Though the histologic changes in this group of cases do not warrant the specific diagnosis of struma lymphomatosa, yet the clinical findings suggest a close relationship to this disease.

Spontaneous myxedema in the adult is accompanied by fibrosis, infiltration of lymphocytes, and oxyphilic changes of the thyroid epithelium that suggest struma lymphomatosa. It is quite possible that struma lymphomatosa represents some type of compensatory response on the part of the thyroid. Under certain conditions this results in a striking enlargement of the thyroid and marked infiltration with lymphocytes, as in the majority of surgical specimens of struma lymphomatosa; however, atrophy and fibrosis may predominate, as in spontaneous myxedema. We have seen 2 cases in which myxedema occurred spontaneously and was associated with an enlarging thyroid and histologic changes characteristic of struma lymphomatosa.

Although we do not as yet have enough evidence to state that the changes found in what we call "lymphoid thyroiditis" and of spontaneous myxedema are respectively the beginning and the end point of struma lymphomatosa, there is some clinical evidence to support the theory of a relationship of these conditions. Certainly in all three, when the goiter predominates, x-ray therapy is of value in reducing its size; and when hypothyroidism is present, the administration of desiccated thyroid to the limit of tolerance may be of value not only in controlling the symptoms of hypothyroidism, but also in diminishing the size of the goiter.

SUMMARY

1). Subacute thyroiditis, struma lymphomatosa, and Riedel's struma are three separate entities that bear no relationship to one another.

2). Confusion in classification has resulted in the reporting of many cases of subacute thyroiditis as Riedel's struma.

3). Since subacute thyroiditis is a self-limited disease in which operation is not necessary, it is important to establish the diagnosis clinically.

4). Biopsy of the thyroid with the Silverman needle is an important aid to the diagnosis of thyroiditis.

5). This method of biopsy is also a valuable aid to the diagnosis of struma lymphomatosa and lymphoid types of thyroiditis and enables the surgeon to establish the diagnosis and in many cases to give effective nonsurgical treatment.

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LIMITATIONS AND INDICATIONS IN THE TREATMENT OF CANCER OF THE THYROID WITH RADIOACTIVE IODINE*†

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THE conventional treatment of a tumor by destructive ionizing radiation is based upon a selective sensitivity of tumor tissue as compared to normal tissue. The treatment of diseased thyroid tissue by radiation from radioiodine is based upon selective concentration of iodine by functioning thyroid tissue. In the former instance tissue sensitivity is the all-important consideration. In the latter instance tissue concentration of the radioactive iodine is the *sine qua non* of treatment. The thyroid avidity for a single element, *i.e.*, iodine, makes it unique among all tissues because of its capacity to concentrate radioactive isotopes in amounts which can be partially to totally destructive to this organ. This is amply demonstrated in the reports from many clinics on the successful treatment of Graves' disease with radioiodine (1, 2, 3, 4). There are also reports (5, 6, 7) of selected cancers of the thyroid which concentrated enough radioactive iodine to exert a cancericidal effect on the tumors.

During the past five years several cooperating investigators at the Memorial Hospital and the Sloan-Kettering Institute have been engaged in physiologic studies of cancer of the thyroid and in evaluating the possible use of radioactive iodine in the treatment of such tumors. Of the 146 patients bearing cancer of the thyroid whom we have studied, it has been desirable and possible to administer therapeutic amounts of radio-

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active iodine to 20. Objective improvement as evidenced by histologic or x-ray evidence of tumor destruction has been observed in 10.

The major discussion at the moment is not of our successes but of the indications and limitations to this type of treatment as we see them at the present time. For the sake of clarity and a logical presentation, we shall first discuss the limitations. On the basis of the limitations as we have analyzed them, we propose to present the indications, as practiced at Memorial Center, for treating cancer of the thyroid with radioactive iodine. The major limitations to this type of treatment are: 1) the relative to absolute lack of natural avidity for I^{131} of practically all cancers of the thyroid, and the natural variability in function of those tumors which do concentrate radioiodine, 2) the iatrogenic impairment to natural or induced avidity for radioiodine of certain tumors, and 3) the damaging effects of the radiation from radioiodine on normal and vital tissues.

The first limitation is demonstrated by the tabulated results of a study done by Fitzgerald and Foote (8) of our institution, which showed that less than 50 per cent of 100 specimens of thyroid cancer picked up measurable amounts of radioactive iodine (Table 1). It is important to note that radioactive iodine was concentrated in only 28 per cent of the papillary carcinomas, which in our clinics, as well as in most clinics, comprise about

TABLE 1. RESULTS OF RADIOAUTOGRAPHIC STUDIES OF 100 CANCERS OF THE THYROID WHICH CONCENTRATED RADIOACTIVE IODINE IN THE TUMORS. (FORTY-SIX PER CENT OF THESE TUMORS CONCENTRATED DEMONSTRABLE AMOUNTS OF THE ISOTOPE.)

Type	No. of cases	+	−
Papillary	29	9	20
Alveolar & follicular	38	28	10
Solid	12	5	7
Hürthle cell	10	3	7
Giant and spindle cell	6	0	6
Anaplastic	3	0	3
Unclassified	2	1	1
Total	*100*	*46*	*54*

50 per cent of all cancers of the thyroid. It is also important to point out that radioactive iodine was not concentrated in any of the 6 giant-cell and spindle-cell carcinomas, which in our experience are the most malignant cancers of the thyroid. In general it can be concluded from the study done by Fitzgerald and Foote that the concentration of radioactive iodine by cancers of the thyroid occurs primarily in those tumors bearing

colloid-filled follicles and only rarely in those tumors not containing colloid. Furthermore, in no instance did any of the functioning tumors in this study concentrate as much I^{131} as did the adjacent normal thyroid tissue. However, in patients having pulmonary or skeletal metastases, we have been able to induce an avidity for radioiodine by total ablation of the normal thyroid and by the administration of thiouracil in large doses. Of 35 patients whose normal thyroids had been totally removed,

FIG. 1. Autoradiogram of a follicular and alveolar adenocarcinoma of the thyroid. Attention is called to the irregular and patchy concentration of I^{131}.

in 21 there developed a significant increase in function of the metastatic lesions (9). By our present criteria only 2 of these showed enough increased avidity for I^{131} to justify administration of the isotope in therapeutic amounts. Twenty-one out of 30 previously totally thyroidectomized patients showed an even greater (in some instances a maximum) avidity for radioiodine after prolonged treatment with thiouracil.

Another natural limitation to the treatment of cancer of the thyroid with radioactive iodine is the fact that the capacity of these tumors to concentrate radioiodine is not uniform. This is illustrated by an irregular pickup of I^{131} in the autoradiograms of many such tumors (Fig. 1). It is

also of considerable interest that various metastatic lesions manifest quite different functional patterns. Oftentimes only one metastatic lesion assumes function. Following treatment of that lesion, another lesion may assume the ability to concentrate I^{131}. This is illustrated by the following case history:

Mrs. L. P., M.H. #95343, a 65-year-old woman, when first admitted to Memorial Center had a follicular adenocarcinoma of the thyroid with metastases to the lumbar and cervical vertebrae, sacrum, ilium, femur and to the seventh, eighth and ninth ribs. A maximum uptake of radioiodine was initiated after total thyroidectomy and prolonged treatment without thiouracil, primarily in the cervical vertebral metastases. After two 25-millicurie doses of radioiodine, the pain in this area improved markedly. Then the uptake of radioiodine, as demonstrated by *in vivo* measurements, shifted to the lumbar and sacral metastases. After a 200-millicurie dose of radioiodine, less than 20 per cent of which was excreted in ninety-six hours, the pain in these areas disappeared and the patient was able to walk for the first time in several years. However, eight months later, a paraplegia developed from extension of the rib metastases, which had assumed a capacity to concentrate I^{131}. She has now received another 100-millicurie dose for the treatment of these lesions and has again experienced subjective improvement. We have, in short, destroyed only certain of the metastases with each dose of radioiodine, and as soon as one area has been controlled, another has assumed a capacity to concentrate I^{131}. Unfortunately, the stimulus to function in this patient has been associated with a stimulus to growth.

Of the iatrogenic limitations to this form of treatment, we might mention the fact that the administration of iodine or certain iodinated radiopaque dyes will interfere with the pickup of radioiodine. Of real importance, however, is that it has been observed that the iodine-concentrating ability of thyroid cancers is surprisingly susceptible to radiation. We have observed in 4 patients whose tumors had acquired a maximum avidity for I^{131} that the administration of non-cancericidal doses of I^{131} markedly decreased the ability of their tumors to concentrate the isotope for some time. This is illustrated by the following case report:

F.M., M.H. #89770, a 13-year-old girl, was first seen at Memorial Hospital in April of 1948 because of a known papillary and follicular adenocarcinoma of the thyroid with nonfunctioning pulmonary and cervical node metastases. Six months following the administration of a "thyroidectomizing" dose of I^{131}, she excreted 60.6 per cent of a tracer dose of I^{131} and was found to be concentrating measurable amounts of radioactive iodine in the metastases. Six months later, she was found to be excreting 59.3 per cent of a tracer and to be concentrating the same degree of radioiodine in the metastatic lesions. At this time, the administration of thiouracil in large doses was begun. Within three months, she was excreting only 28 per cent of the dose. This degree of function continued without further improvement for another five months at which time, it was planned to administer several 25-millicurie doses of I^{131}. Of the first therapeutic dose, she excreted 38 per cent. Unfortunately, following this first therapeutic dose which exerted no objective beneficial effects on either the cervical or pulmonary metastases, the functional capacity of the tumor decreased. Within three weeks, after administering

the first therapeutic dose, she was excreting 75 per cent of a test dose. Notwithstanding the good effect induced by thiouracil prior to the first therapeutic dose, continued treatment with thiouracil for one year has decreased the urinary excretion of radioiodine very slowly from 73 per cent to 47 per cent (Fig. 2).

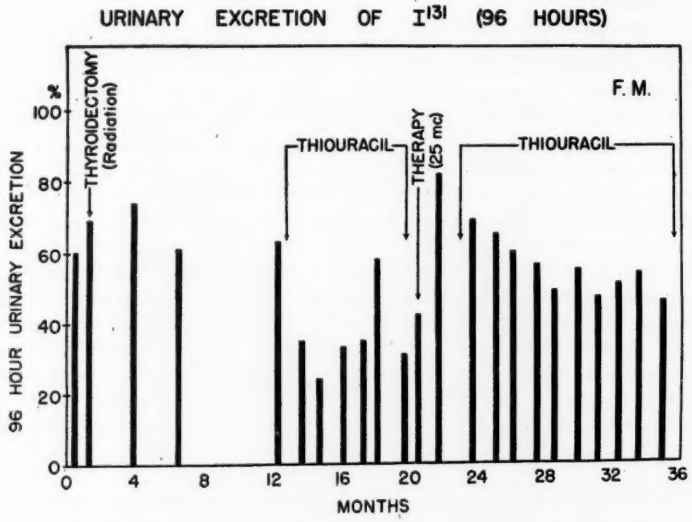

FIG. 2. The urinary excretion of tracer doses of I^{131} in F. M. before and after treatment with 25 millicuries of I^{131}. The solid bars represent the urinary excretion of I^{131} in ninety-six hours after each tracer. It is to be noted that the first treatment with thiouracil resulted in a comparatively rapid fall in urinary excretion of I^{131}. However, after treatment with 25 mc. of I^{131} there developed a marked increase in the urinary excretion of I^{131} and a very slow recovery of function after treatment with thiouracil.

We have also observed that therapeutic x-radiation is effective in diminishing the ability of these tumors to concentrate radioactive iodine. This is illustrated in the following case history:

D.B., M.H. #101328, a 60-year-old male, was first seen at Memorial Center in July 1950, at which time he was found to have a papillary and follicular carcinoma of the thyroid with diffuse pulmonary metastatic disease. In an attempt to induce iodine-concentrating ability in the metastases, a total thyroidectomy was performed. Prior to the thyroidectomy, no concentration of I^{131} in the pulmonary metastases was demonstrable. Two months following the total thyroidectomy, there still was no evidence that the metastases were concentrating I^{131}, and he was excreting 72 per cent of a tracer dose in forty-eight hours. At that time, the patient began taking thiouracil, 1.5 Gm. daily. One month later, he excreted 49.6 per cent of a tracer dose of I^{131} in forty-eight hours, and was found, by *in vivo* measurements, to be concentrating significant amounts of radioactive iodine in the region of his pulmonary metastases. However, because of the patient's dyspnea and hemoptysis, he was treated with x-ray. He received 326 r daily

for a total of 2282 r. This was administered anteriorly and posteriorly through 18 by 16 cm. ports with a 1,000 KV machine utilizing 3 milliamperes.

After finishing the x-ray treatment, another tracer of I^{131} was administered. Of this tracer, he excreted 61.6 per cent in forty-eight hours and there was no localization anywhere in the chest (Fig. 3). This change in function in the metastatic lesions we have interpreted as the result of the therapeutic x-radiation directed at the pulmonary lesions.

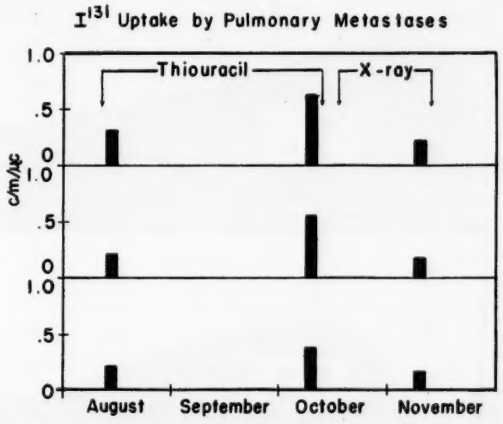

FIG. 3. The effect of x-radiation on pickup of I^{131} by three pulmonary metastases from carcinoma of the thyroid. The three horizontally blocked sections represent observations made on three separate metastatic areas in the chest. The solid black columns represent the counts per minute divided by millicuries of I^{131} administered. It is to be noted that treatment with thiouracil resulted in an increased pickup of I^{131} and that following the administration of therapeutic x-radiation the function of these tumors decreased to a minimal level.

The damaging effects of radiation from radioiodine which may occur in normal and vital tissues constitute a serious limitation to the treatment of cancer of the thyroid with this agent. Although we have been unable to demonstrate a significant concentration of radioactive iodine in any tissues other than the thyroid, an administered therapeutic dose of I^{131} will be transported in the blood or extracellar fluids until it has been picked up by functioning thyroid tissue or excreted via the urinary tract. If the functional capacity of the tumor tissue is minimal, nonthyroidal tissues will be exposed to a large percentage of the radioiodine as it is transported through the extracellular space. On the other hand, if the tumor possesses a maximum capacity to concentrate and to retain the isotope, most of the radiation will be delivered to the tumor, whereas those tissues bathed by the extracellular fluid will be exposed to less of the administered isotope. Of course, if the tumor concentrates the iodine maximally, but

rapidly secretes it as thyroid hormone, the amount of radiation delivered to the tumor will be less and that delivered to nonthyroidal tissues will be increased (Figs. 4 and 5). Thus it can be seen that the radioactivity carried in the extracellular fluid, if great enough, may produce radiation effects on other tissues.

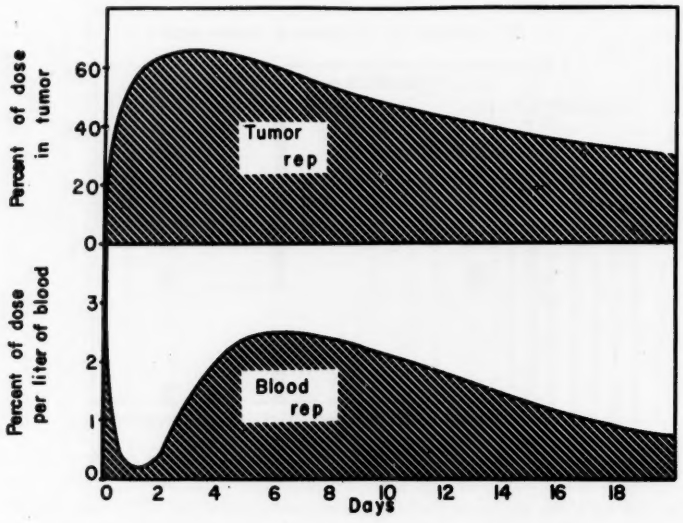

FIG. 4. A theoretical graph illustrating the radiation of tumor tissue *vs.* radiation of blood. It is to be noted that if the tumor has a high avidity for iodine the I^{131} leaves the blood rapidly and enters the tumor. If the tumor loses the I^{131} rapidly, either as the result of secretion of thyroid hormone or as the result of tissue breakdown, there is a rather significant increase in blood level with a fall in tumor radiation.

Those extrathyroidal tissues which would seem more vulnerable are the kidney, liver, gonads, and blood-forming organs. Extensive studies by Dr. Lee Farr and associates on several of these patients have failed to reveal any radiation-induced renal damage. Similarly, liver function studies done on several of these patients have failed to reveal any significant radiation effect on this organ. Only 3 out of 12 menstruating women manifested transient amenorrhea after receiving relatively large doses of I^{131}.

Some degree of radiation damage to the formed elements of the blood or blood-forming organs has been noted, however, in all of our patients who have received therapeutic doses of radioactive iodine. The hematologic changes have varied from a transient fall in the lymphocytes to a lethal pancytopenia. The latter was observed in 1 patient who received 638 millicuries of I^{131} in fourteen months, which amount was calculated to

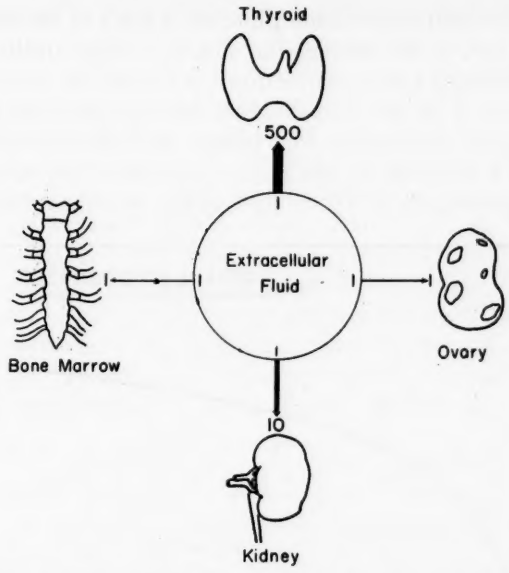

FIG. 5. A theoretical illustration demonstrating the more important tissues which may be irradiated as the result of high levels of I^{131} in the extracellular fluid space. If the pickup of radioiodine is minimal, the radioactivity in the extracellular fluid space is greater. Likewise a rapid release of iodine as thyroxine or as thyroglobulin will also result in a high level of radioactivity in the extracellular fluid space, with radiation to nonthyroidal tissues.

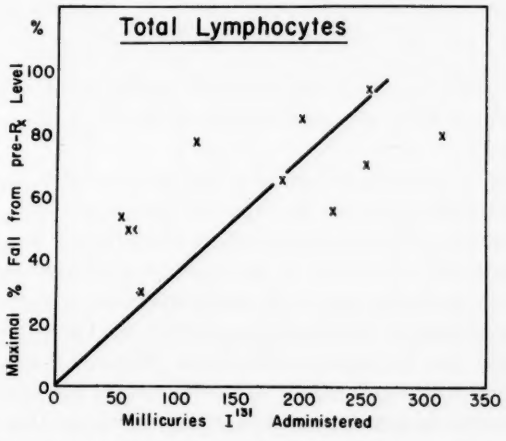

FIG. 6. The percentile fall in total blood lymphocyte count per millicurie of I^{131} administered. Attention is called to a poor correlation.

deliver 1300 roentgen equivalents physical (r.e.p.) to the total body.

Changes in the blood hemoglobin did not occur until some months after administering the therapeutic doses of I^{131} and, in no instance, represented more than a 26 per cent decrease from pretreatment levels. However, studies with radioactive iron before and after treatment with I^{131} have revealed a decrease in the apparent rate of hemoglobin synthesis after the administration of I^{131} in therapeutic amounts. Furthermore, we

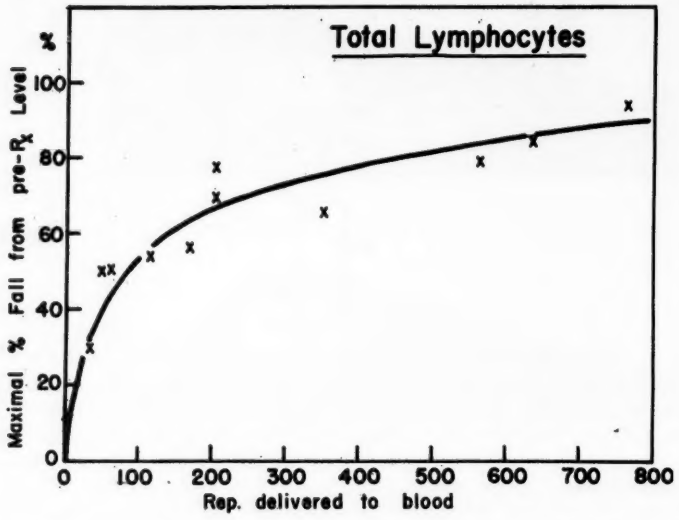

FIG. 7. The percentile fall in total blood lymphocyte count per r.e.p. delivered to the blood. Correlation is good.

have observed that the fecal and urinary excretion of coproporphyrin I and III is increased after the administration of I^{131} in doses as small as 10 millicuries (10).

Although we have often observed a fall in the total neutrophil count following the administration of therapeutic amounts of I^{131}, the changes in this index are not as sensitive to the effect of radiation as are the changes in total lymphocytes. However, if we attempt to correlate the percentile fall in circulating lymphocytes with the millicuries of radioiodine administered, the correlation is not a good one (Fig. 6). On the other hand, we have determined the roentgen equivalents physical (r.e.p.) delivered to the blood by daily determinations of radioactivity per unit of blood and and have been able to get a good correlation between this factor and the percentile fall in the total lymphocyte count (Fig. 7). It is apparent then that damage to the blood and the blood-forming tissues can be correlated

with the integrated concentration of radioiodine in the blood subsequent to the administration of a large dose of this radioisotope.

As was indicated earlier, we can induce a maximum avidity for I^{131} in many metastatic tumors by administering thiouracil in large doses over fairly long periods of time to patients whose normal thyroids have been removed. In such settings, when radioactive iodine is administered in even fairly large doses, the blood and extrathyroidal tissues are usually spared from any serious radiation effects. Exceptions to this generalization have been observed in 2 patients whose tumors concentrated enough I^{131} to justify the administration of large doses of this isotope without resorting to total thyroidectomy or prolonged treatment with thiouracil. In both of these patients the radiation effects on the tumors were great enough to cause a breakdown of tissue and release of radioactive thyroid hormone. This phenomenon is illustrated by the following case history:

A.G., M.H. #103509, a 59-year-old female, was first seen at Memorial Center in November of 1950 complaining of massive hemoptysis on three different occasions, during the two months prior to her admission. She had had a nontoxic goiter removed in 1926 and also in 1945. In 1949, the goiter recurred again. On admission, she was found to have a firm 6×6 cm. nodule in the midline of her neck at the level of her thyroid, which was fixed firmly to the skin and to the underlying tissues. The patient had a warm, moist skin, a fine tremor of the extended fingers and a pulse rate of 88 per minute. Her basal metabolic rate was plus 24 per cent and the serum protein-bound iodine was 14.5 micrograms per cent. X-ray examination of the chest revealed diffuse minimal nodular

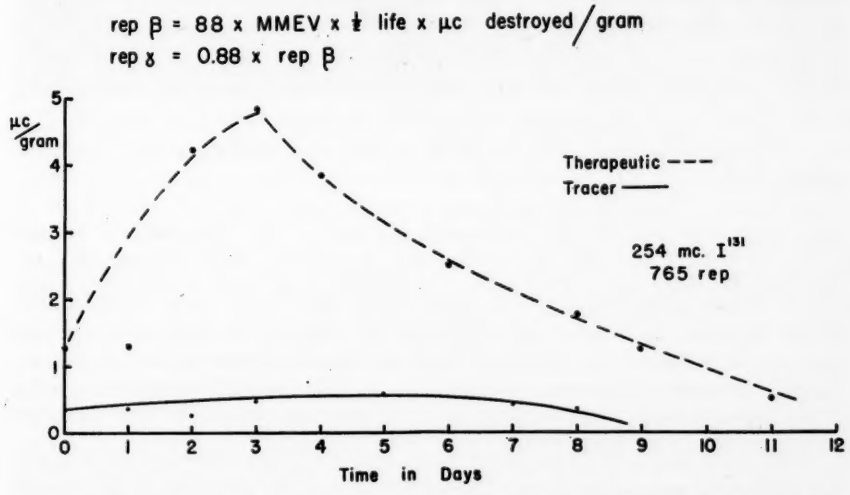

FIG. 8. Blood levels of I^{131} following tracer and following therapeutic dose of I^{131}. Maximum level following a tracer was 0.6 microcuries/gram of blood; and following therapeutic dose of I^{131}, 4.6 microcuries/gram of blood.

densities consistent with the picture of pulmonary metastases from cancer of the thyroid. On reviewing specimens taken from the thyroid removed in 1945, the diagnosis of an alveolar and follicular carcinoma of the thyroid was made.

She excreted only 26.7 per cent of a tracer dose of radioiodine in forty-eight hours. At that time she was found to have concentrated 13 per cent of the tracer in her neck and to have a high degree of radioactivity over the chest, *i.e.*, up to 15.9 counts per minute per administered microcurie at skin contact. (Background measurements with the tube used were 0.1 counts per minute per microcurie.) Blood levels following a second tracer of I^{131} showed a maximum of 0.32 per cent of the dose per liter of blood. On the

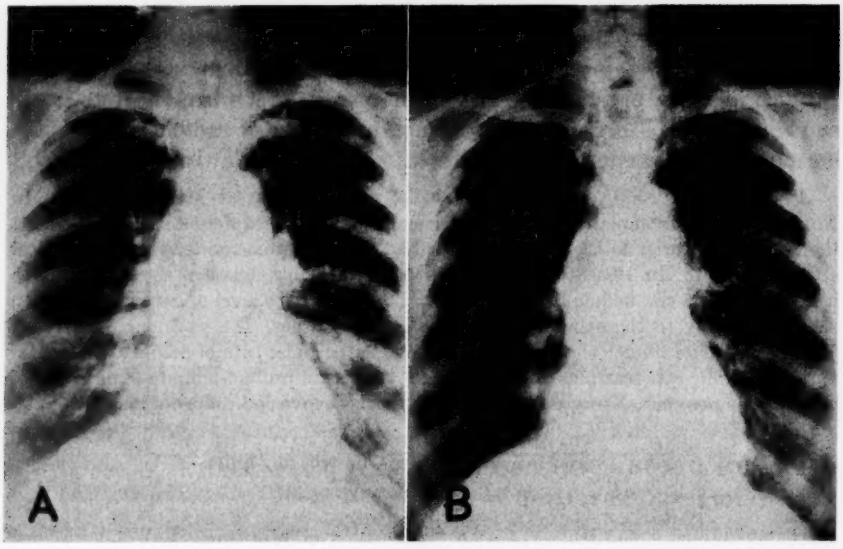

FIG. 9. A. Chest roentgenogram of A. G. on admission. B. Chest roentgenogram of A. G. seven weeks after administering therapeutic dose. Note decrease in nodularity of lung tissue.

basis of these findings, it was calculated that a dose of 250 millicuries of I^{131} would deliver between 90 and 100 r.e.p. to the blood. Accordingly, on January 4, 1951, she was given 254 millicuries of I^{131}. Of this, she excreted 31 per cent in forty-eight hours. Much to our surprise, however, the level of radioactive iodine in her blood reached a maximum of 2.5 per cent of the dose per liter. Contrary to our previous calculations, 765 r.e.p. were delivered to the blood during the effective life of the isotope (Fig. 8). Transient nausea and vomiting developed, as did also a marked lymphopenia and a rather alarming fall in the total white count. Interestingly enough, the latter appeared to be benefited by the administration of ACTH.

The post-treatment blood I^{131}, which reached an alarmingly high level, was found to be primarily protein-bound. It is of interest that only 12 per cent of the protein-bound radioactive iodine was butanol-soluble. The remaining fraction, upon hydrolysis, released thyroxine and diiodotyrosine in proportions similar to those observed after hydrolysis of thyroglobulin. It seems likely, therefore, that the marked rise in blood I^{131} which

occurred after administering the therapeutic dose, occurred as the result of a breakdown of tissue, rich in thyroglobulin, subsequent to the radiation. This thesis is supported by the very striking change which occurred in the patient's chest roentgenogram within six weeks after administering the therapeutic dose of I^{131} (Fig. 9).

In view of the limitations outlined above, we have defined the following indications for the treatment of cancer of the thyroid with radioactive iodine: 1) that the tumor be not removable by a competent surgeon, 2) that the tumor be capable of concentrating enough radioactive iodine to exert a cancericidal effect, and 3) that the calculated total body irradiation delivered by the proposed therapeutic dose of I^{131} be within the range of safety.

Notwithstanding the fact that we should welcome a physiologic treatment of this disorder, cancer of the thyroid is a surgical disease which, if possible, should be treated by adequate removal of the primary disease and of the adjacently involved tissues. We believe that treatment with radioactive iodine for cancer of the thyroid which is localized to the thyroid and adjacent lymph nodes and which can be removed by competent surgeons is indefensible.

Since it has been amply demonstrated that those tumors which do collect radioactive iodine concentrate less than that which is retained by normal thyroid tissue, we believe that radioactive iodine should not be administered therapeutically to patients with cancer of the thyroid until a maximum avidity for the radioiodine has been induced. We have already stated that total removal or destruction of the normal thyroid results in an increased avidity for radioiodine in about 50 per cent of all patients having metastatic cancer of the thyroid. We have also reported that the administration of thiouracil in large doses for several months to previously totally thyroidectomized patients causes a maximum pickup of I^{131} in about 70 per cent of patients treated in this fashion. Although our experiences to date suggest that those tumors which do assume a marked avidity for I^{131} after the institution of these procedures usually manifest some follicular structure, the exceptions to this rule have been frequent enough to justify subjecting all patients with distant metastases to removal of the normal thyroid and to prolonged treatment with thiouracil in an attempt to bring them to a treatable stage with radioactive iodine. At the present time, we do not administer therapeutic doses of I^{131} to these patients until the 48-hour urinary excretion of a test dose is 30 per cent or less. From these studies, we are able to determine the amount of a therapeutic dose which will be retained presumably by the tumor. It can be seen from Table 2 that the percentage excreted even of a large therapeutic dose is comparable to the amount excreted of a previous tracer dose.

TABLE 2. THE URINARY EXCRETION OF TRACER DOSES AND THERAPEUTIC DOSES OF I^{131}. (IT IS IMPORTANT TO NOTE THAT THE EXCRETION OF A THERAPEUTIC DOSE OF I^{131} IN ALL CASES WAS APPROXIMATELY THE SAME AS THAT OF A PRETREATMENT TRACER.)

No. of doses	Mean dose	96-Hour mean urinary excretion	
		Tracer	Therapy
37	124 mc.	47%	50%
	Doses greater than 100 mc.		
21	185 mc.	46%	49%
	Doses less than 100 mc.		
16	45 mc.	52%	52%

In view of the toxic effects that circulating radioiodine may exert on normal and vital tissues, we believe that every candidate for treatment with large doses of I^{131} should have prior tracer studies with daily determinations of the blood levels for at least ninety-six hours. From these figures, which we plot graphically, we are able to calculate the total number of roentgen equivalents physical (r.e.p.) which will be delivered to the body from circulating I^{131}. In our final determination of a dose of I^{131}, we keep the amount of radioactive iodine down to a level which is calculated to deliver less than 500 r.e.p. to the blood.

By adhering to these criteria, we have been able to administer radioactive iodine in effective and relatively safe amounts to 16 patients with metastatic cancer of the thyroid. The following case history, we believe, illustrates the desirability of adhering strictly to the above indications:

W.M., M.H. #87060, a 15-year-old white male, was admitted to Memorial Hospital in May of 1947. He was found to have a low-grade follicular adenocarcinoma of the thyroid with diffuse pulmonary metastases, which on x-ray examination appeared as miliary nodular densities throughout both lung fields. He was also found to have rheumatic heart disease with a grade 4 mitral stenosis. A preliminary tracer study revealed no measurable uptake of radioiodine in the pulmonary metastases. In September 1947, a thyroidectomizing dose of I^{131} (25 mc.) was administered. Following a test dose in April 1948, he was found to be concentrating significant amounts of I^{131} in the pulmonary lesions. At that time, prolonged treatment with thiouracil, up to 1.5 Gm. daily, was undertaken. This program was continued until December 1948, when he was found on two occasions to excrete in the urine less than 5 per cent of a tracer dose of I^{131} which had been given forty-eight hours after stopping administration of the thiouracil. On December 29, 1948, a therapeutic dose of 112 millicuries was administered. Only 6 per cent of this dose was excreted during the first ninety-six hours and the blood level did not rise above 0.67 per cent of the dose per liter of blood. On the basis of these observations, it was calculated that his blood received, during the effective life of the administered radioiodine, 208 r.e.p. of radiation. As the result of this radiation, there occurred a 70 per cent decrease in total lymphocytes but no significant decrease in total white count. Serial roentgenograms of the chest showed a progressive decrease

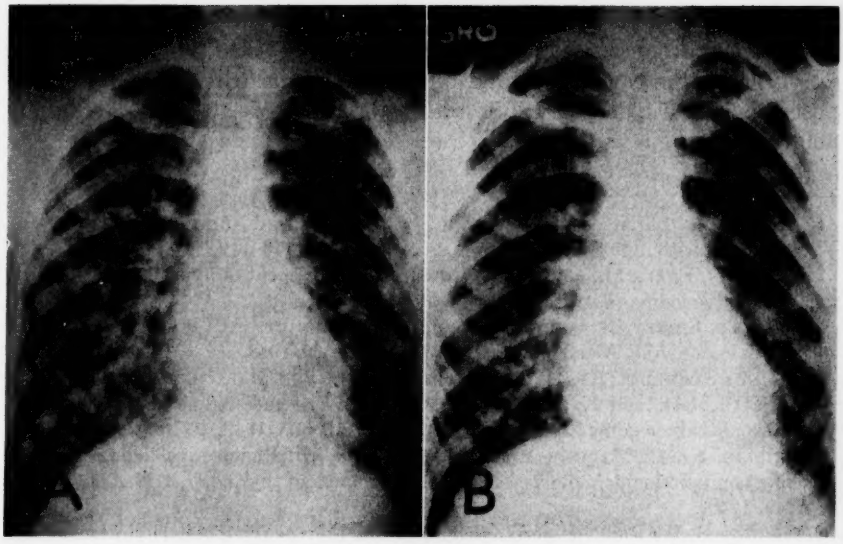

FIG. 10. A. Chest roentgenogram of W. M. before the administration of I^{131} in a therapeutic dose. B. Chest roentgenogram of W. M. nineteen months after administering 112 millicuries of I^{131}, 6 per cent of which was excreted in ninety-six hours.

in tumor mass, which was maximum by July of 1950. Notwithstanding this striking improvement, he still has the disease which again, after acquiring a maximum avidity for I^{131}, was treated in February of 1951.

SUMMARY

1. The limitations to the treatment of the thyroid with radioactive iodine are defined as follows:

a. The relative to absolute lack of natural avidity for I^{131} of practically all cancers of the thyroid and the natural variability in function of those tumors which do concentrate radioiodine.

b. The physician-induced impairment to natural or induced avidity for radioiodine of certain tumors, *i.e.*, by the administration of iodine or iodine-containing drugs or by the administration of non-cancericidal amounts of radiation, isotopic or x-ray.

c. The damaging effects of the radiation from radioiodine on normal or vital tissues, *i.e.*, the blood and blood-forming organs.

2. The indications for the treatment of cancer of the thyroid with radioactive iodine are defined as follows:

a. That the tumor be not removable by a competent surgeon.

b. That the tumor be capable of concentrating enough radioactive

iodine to exert a cancericidal effect. Methods of inducing this function in such tumors are discussed.

c. That the calculated total blood irradiation delivered by the proposed therapeutic dose of I^{131} be within the range of safety, *i.e.*, less than 500 r.e.p.

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THE TRACER DOSE OF RADIOACTIVE IODINE IN THE DIAGNOSIS OF THYROID DISEASE*

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THIS effort to evaluate the clinical importance of the tracer dose of radioactive iodine in the diagnosis of diseases of the thyroid is based upon an analysis of the findings obtained in a clinical laboratory in an ordinary general hospital. The patients were practically all private patients referred to the laboratory as out-patients, for diagnosis or for a tracer dose preparatory to treatment. They probably represent fairly accurately the type of patients referred to any isotope laboratory by any unselected group of practitioners. Our errors in carrying out the procedures and the inconsistency of some of the findings also probably can be expected from an ordinary clinical laboratory.

METHOD

General. The 24-hour pickup of I^{131} by the thyroid gland and the 24-hour urinary excretion were determined on all patients. In about half the patients, blood was drawn at the end of twenty-four hours to determine the total plasma I^{131} and the protein-bound fraction (PBI^{131}). The ratio between these two was also calculated. Our investigation was limited strictly to the following five factors: 1) the 24-hour thyroid pickup of I^{131}; 2) the 24-hour urinary output; 3) the plasma I^{131}; 4) the protein-bound fraction of I^{131}; and 5) the ratio of protein-bound I^{131} to I^{131} in plasma.

The tracer dose. A 50-microcurie dose was used in all cases. If the procedures are limited to only pickup and excretion, a lesser quantity is sufficient, but whether it would permit of accurate blood determinations we do not know. A 50-microcurie dose of carrier-free I^{131} is measured out and placed in a 25-ml. volumetric flask. Distilled water is added to increase the volume to exactly 25 ml. Each dose is assayed at three distances, chosen so that the second distance gives half the number of counts given

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by the first or shortest distance; and the third distance, one-third the number of counts. These distances as measured from the center of the flask (the center of radiation) to the center of sensitivity of the Geiger-Mueller counter tube are 1) 23.5 cm.; 2) 33.5 cm.; and 3) 41.0 cm. If the measurement is made from the front of the 25-ml. flask to the tube, it will simulate almost exactly the measurement from the skin to the tube. The center of radiation in a 25-ml. flask is approximately 2 cm. from the front of the flask, and the center of radiation of the thyroid gland is only a trifle over 2 cm. from the skin surface. Thus, if one assays a quantity of I^{131} in a 25-ml. flask at a distance measured from the front of the flask to the tube, one should obtain practically the same number of counts as obtained for the same quantity of I^{131} in the thyroid gland at a distance measured from the skin to the tube. The isthmus of the thyroid gland crosses the trachea just below the cricoid cartilage. The skin measurement is taken from a point on the center of the neck 1 cm. below the cricoid cartilage. All three measurements are used in the calculations. It would be probably more accurate to use only the counts from the two furthest distances.

The Geiger counter is calibrated and the number of counts per microcurie is known. The presumed 50-microcurie dose is corrected to 48 or 52 microcuries or to whatever the reading indicates. This correction is not necessary in the calculation of thyroid pickup, which is entirely a percentile relationship of two sets of counts, but it is useful in calculating percentage of urinary output, which is a percentile relationship between the number of microcuries given as determined by one counter and the number excreted as determined by another counter.

The dose is given in the morning, preferably with the patient fasting. It is not essential that the patient fast completely. We have found that an empty stomach plus the nervousness accompanying the visit to the laboratory and in the drinking of the "atomic cocktail" occasionally induce vomiting. Radioactive vomitus is definitely a nuisance. A piece of toast and a cup of coffee do not interfere with the 24-hour determinations and eliminates the vomiting episodes.

The patient must not be taking thyroid medication, antithyroid drugs or iodine. If he is receiving antithyroid therapy with iodine or propylthiouracil, it is discontinued for one week. The dye used in an x-ray examination of the gallbladder interferes for about three weeks, and desiccated thyroid for about the same length of time.

The Geiger-Mueller counter. In all these determinations a bismuth-wall gamma-ray counter, measuring 1 inch $\times$ $8\frac{1}{2}$ inches, was used. Its high efficiency for iodine gamma-ray counting makes it necessary to use an absorber to eliminate scattered radiation. The tube is enclosed in a $\frac{1}{2}$-inch lead shield with an opening in the side as long and as wide as the bismuth

cathode screen. Over the opening is placed a sheet of lead, 1.2 Gm./cm.^{2} (.045 inch thick), to act as an absorber. In a mock-up study, a hollow glass thyroid was blown up to simulate a normal thyroid gland. Twenty-five microcuries of I^{131} was placed in it and the glass thyroid was suspended in a 1,000-ml. beaker with the front of the simulated gland 1 cm. from the inner wall of the beaker. Counts were taken without an absorber, both with the beaker empty and with the beaker full of water. When the beaker was filled with water, there was almost a 25 per cent increase in counts due to scatter. These secondary waves are much weaker than the I^{131} gamma waves and can be removed by absorption. If a sheet of lead, 1.2 Gm/cm.^{2}, is placed in front of the tube the counts are identical both when the beaker is empty and when it is full of water. In short, the absorber eliminates the spurious counts without too much reduction (30 per cent) in the total number of counts. This experiment was repeated by removing the thyroid gland from a fresh cadaver and replacing it with the glass model filled with a solution of I^{131}. The results were the same. In counters of low efficiency the scattered rays and spurious counts are not too important but with tubes of high efficiency the error is quite large.

We use the tube in a longitudinal direction over the neck. The findings are practically the same whether the tube is placed transversely or longitudinally but since the variation of the position of the thyroid gland is more in an up-and-down rather than a transverse direction, a rectangular shaped portal gives better results if placed parallel with the longitudinal axis of the neck.

Calculation of thyroid pickup. Counts are made over the neck at three distances as measured from the skin to the center of the tube, 1) 21.5 cm.; 2) 31.5 cm., and 3) 40.0 cm. With a 10 per cent pickup (5 microcuries) the net counts are in the neighborhood of 1) 600; 2) 300, and 3) 200 per minute. All of our counts are registered for two minutes. When the pickup is low, the time is increased to give a minimum of 500 net counts at the furthest distance.

A count is taken with the tube against the thigh. This reading is deducted from the thyroid readings, as representing background and soft tissue radiation. In a large series of readings the counts from the second distance have averaged exactly half of those from the first distance; and from the third distance they have averaged a third of those from the first distance. There have been, of course, sharp variations. If the second and third counts are higher than the respective 50 per cent and 33 per cent, the thyroid gland is more deeply placed than estimated; if the second and third counts are less than 50 per cent and 33 per cent, the gland is closer to the skin than was estimated.

A correction can be made for this error by mathematical calculation or

by actually measuring the percentage shifts in the second and third counts when a center of radiation is shifted one to three centimeters. Most of our determinations were not corrected in this manner. The sum of the corrected readings is divided by .91 to correct for decay and then compared to the counts made on the sample on the previous day.

Calculation of urinary output of I^{131}. Two hundred milliliters of urine is placed in a Marinelli beaker and counted through a calibrated cylindrical tube. The number of microcuries excreted is calculated, corrected for decay

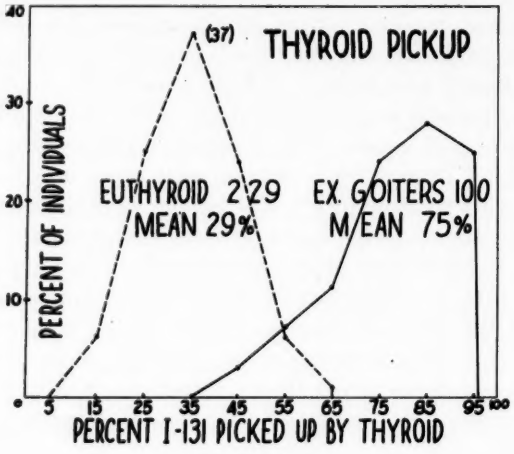

FIGURE 1

and compared to the number of microcuries administered as determined by the preliminary assay with the bismuth-cathode counter.

Total and protein-bound I^{131} of plasma. One milliliter of plasma is placed in a small steel planchette, dried slowly under an infra-red lamp, and counted in a flow-gas counter in the Geiger region, using helium and alcohol vapor as the gas. Calibration of such a counter is none too accurate. The dried blood in itself absorbs 50 per cent of the radiation. The protein-bound I^{131} was determined according to the method described by Clark, Moe and Adams (1). This consists essentially of precipitating the protein with trichloracetic acid, washing, drying, and counting.

ANALYSIS OF FINDINGS

Primary exophthalmic goiter and euthyroidism

Thyroid pickup. Figure 1 compares the findings in 229 presumably euthyroid individuals with those in 100 patients with exophthalmic or toxic diffuse goiter. The mean and also the median pickup of I^{131} in the euthyroid

individuals was 29 per cent of the administered dose. Eighty-six per cent of the euthyroid subjects picked up between 15 and 45 per cent of the dose. There is a variation of from 5 to 55 per cent. Some of this variation is undoubtedly due to errors in technique and some to errors in diagnosis. A low pickup can be found in any normal person who is taking iodine in any form and, in spite of careful checking, it is easily possible for this to occur. It must be remembered too that these so-called euthyroid individuals were not normal people taken from the healthy population, but were

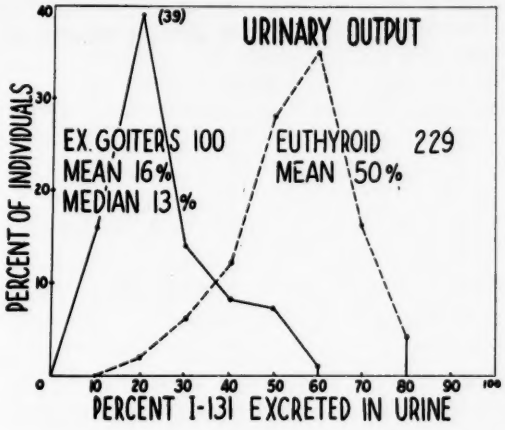

FIGURE 2

largely patients referred to the laboratory for the test. We have labeled them euthyroid with as much care as possible, but it is easily conceivable that a few cases of hypothyroidism and of hyperthyroidism are included in this group. There were 4 individuals with a pickup of 50 per cent or over, who by all clinical criteria were not hyperthyroid. Some of the variation, however, is due to the simple fact that the functional activity of the thyroid gland in picking up iodine has a large normal biologic range.

The mean and also the median pickup for the patients with exophthalmic goiter is 75 per cent. Ninety per cent of these individuals had a pickup between 55 and 95 per cent. This group included only primary exophthalmic or toxic diffuse goiters and not postoperative recurrent goiters or toxic nodular goiters. There were 10 patients with a pickup below 55 per cent. Most of these were not very ill; indeed, in a few, the diagnosis of exophthalmic goiter could be questioned. We did not have a single patient with a frank exophthalmic goiter who did not have a high pickup. The degree of pickup, however, did not vary much with the severity of the disease. If the patient really has the disease, the pickup is high and it may

be just as high in a patient with moderate symptoms as in one with severe symptoms.

Our figure of 75 per cent for the average pickup in toxic diffuse goiter is higher than the 69 per cent reported by Shipley *et al.*(2) and the 51 per cent reported by Werner *et al.* (3) for hyperthyroidism. We believe that our higher figure is due to the exclusion of the toxic nodular goiters, in addition to differences in technique.

TABLE 1. TOTAL PLASMA I^{131} IN 116 EUTHYROID SUBJECTS

Microcuries per liter	Subjects showing values in given range	
	Number	Per cent
.01	27	23
.10	56	48
.20	15	13
.30	10	9
.40	1	1
.50	3	3
.60	2	2
.84	1	
1.20	1	

Mean— .19
Median—.14

Urinary output. Figure 2 shows the urinary output of I^{131} in the same two groups of patients. The euthyroid individuals had an average output of 50 per cent, with a range between 17 and 79 per cent. Seventy-seven per cent of the results fell between 35 and 60 per cent. The exophthalmic goiter patients had a mean output of 16 per cent, with a range between 2 and 52 per cent. Eighty-four per cent of the values fell between 2 and 30 per cent. It is to be noted that in the euthyroid person, by adding the thyroid pickup and the urinary output, we account for only 79 per cent of the total dose, whereas in the patient with exophthalmic goiter we account for 91 per cent. Indeed, in the latter group we occasionally account for more microcuries than we give! This difference between the two groups is due in a large measure to the fact that urinary excretion in exophthalmic goiter is practically completed during the first twenty-four hours but in euthyroid persons continues during the second twenty-four hours (4) (5).

As a diagnostic test the urinary output is reasonably accurate. There is a little more overlap than with thyroid pickup, which can be explained in part by the errors in urinary collection. Fortunately most of the excre-

TABLE 2. TOTAL PLASMA I^{131} IN 55 PATIENTS WITH EXOPHTHALMIC GOITER

Microcuries per liter	Patients showing values in given range	
	Number	Per cent
.01–.09	13	24
.10–.19	14	25
.20–.29	9	16
.30–.39	9	16
.40–.49	4	7
.50–.59	3	5
.80	1	
1.3	1	
2.08	1	

Mean— .29
Median—.21

tion takes place during the first eighteen hours and most of the errors in obtaining an exact 24-hour output occur in the final collection. All in all, the two determinations—pickup and output—are in fairly close agreement.

Ratio of total plasma I^{131} to protein-bound I^{131}. In Table 1 is a summary of the total plasma I^{131} values in 116 euthyroid subjects. In Table 2 are the findings in 55 patients with exophthalmic goiter. The total plasma I^{131} is higher in exophthalmic goiter, but the increase is so little and the

TABLE 3. PROTEIN-BOUND I^{131} IN 116 EUTHYROID SUBJECTS

Microcuries per liter		Subjects showing values in given range	
		Number	Per cent
.001	.009	27	23
.01	.019	44	38
.02	.029	18	15
.03	.039	15	13
.04*	.049	3	2
.05	.059	3	2
.06		1	
.09		1	
.12		1	
.16		1	
.20		1	
.23		1	

Mean— .027
Median—.015
* The level dividing normal from abnormal.

spread is so enormous that the test, as we performed it, has little value. Rollman and Petit (6) came to the same conclusion. In Table 3 is an analysis of the protein-bound I^{131} (PBI^{131}) in 116 euthyroid persons. There are several rather disconcerting observations to be made concerning these statistics. First, there is over one hundredfold variation between the low and the high quantities. Second, the first value listed in Table 3—.001 to .009 microcuries of I^{131} per liter—actually is less than the method can measure. At .01 microcurie per liter our set-up gives 17 counts per minute, which is a little less than the background count. Time will not permit us

TABLE 4. PROTEIN-BOUND I^{131} IN 55 PATIENTS WITH EXOPHTHALMIC GOITER

Microcuries per liter		Patients showing values in given range	
		Number	Per cent
.012	.029	4	7
.03	.039	6	11
.04*	.059	7	13
.06	.079	5	9
.08	.099	4	7
.10	.199	14	25
.20	.299	5	9
.30	.399	4	7
.40	.499	3	5
.67		1	
1.04		1	
1.5		1	

Mean— .109
Median—.106
* The level dividing normal from abnormal.

to count samples for longer than ten minutes. The number of counts is not sufficient to be statistically accurate until we reach .03 μc/liter. Third, a flow-gas counter operated in the Geiger region is a tricky instrument, subject to many discrepancies. And last, we firmly believe that the high readings are definite errors in technique, but in the analysis of any diagnostic method technical errors must be included.

Table 4 shows the PBI^{131} in exophthalmic goiter. In spite of the inaccuracies inherent in the method, if the figure .04 μc/liter be taken as a dividing line, 89 per cent of the euthyroid subjects lie below this figure and 88 per cent of the patients with exophthalmic goiter lie above it. It is clearly a better diagnostic criterion than total plasma I^{131} but in our opinion is too erratic to be reliable.

Chaikoff (7), on the basis of animal experiments, suggested that the rate of conversion of injected I^{131} into PBI^{131} of plasma is a useful guide to thyroid activity. Williams (8) repeated the test in humans. Clark (1) actually used the ratio between PBI^{131} and total plasma I^{131} as a diagnostic test. Sheline (9) reported the conversion ratio was 3 per cent to 41 per cent in 28 euthyroid subjects and over 45 per cent in 16 hyperthyroid patients. Harsha (10) found that those subjects with a conversion ratio of over 50 per cent were hyperthyroid and those with a ratio of less than 10 per cent were hypothyroid. Figure 3 shows a comparison of this ratio in the euthy-

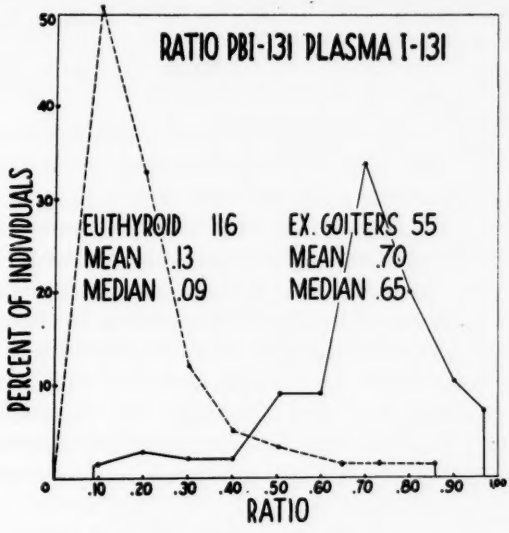

FIGURE 3

roid subjects and in the patients with exophthalmic goiter. It seems to be diagnostic and there is little overlap. From a statistical point of view, the ratio between the quantity of I^{131} bound to protein (presumably the thyroxine fraction) and the total plasma I^{131}, is the best single diagnostic test. However, it is not sufficiently superior to justify the extra labor involved, so we now reserve the determination for those patients whose pickup or output falls in the borderline group. For this purpose it is very useful.

Recurrent exophthalmic goiter

We tested 21 patients with recurrent exophthalmic goiter. The findings are not as clear cut as in the preceding groups. The pickup of I^{131} is shown in Table 5. It varies all the way from 13 per cent to over 90 per cent. It was our opinion that the patient with the 13 per cent pickup had recurrent

TABLE 5. THE THYROID PICKUP IN RECURRENT EXOPHTHALMIC GOITER

Per cent of pickup	Number of patients
13	1
39	1
40– 49	3
50– 59	7
60– 69	3
70 –79	4
90–100	2
Total	21

Mean— 59 per cent.
Median—58 per cent.

hyperthyroidism. Her basal metabolic rate was only +15 per cent; she had a partially decompensated heart with auricular fibrillation and she showed no improvement following a therapeutic dose of I^{131}. It is possible her symptoms were due to previous damage to the heart. The pickup was highest in those patients with palpable recurrence of the goiter and less in those without much enlargement. The urinary output of I^{131} varied from 9 to 59 per cent with a mean of 26 per cent and a median of 24 per cent. Blood was examined in only 9 patients. The plasma I^{131} and PBI^{131} were elevated but to a less extent than in primary exophthalmic goiter (Table 8). Clark's conversion ratio was again fairly accurate, averaging 0.57.

Acute thyroiditis

In Table 6 are the findings in 6 cases of acute thyroiditis. The duration of the disease in these patients was from one to three weeks. This is the period in which the basal metabolic rate is elevated slightly. The disease is characterized by a very low pickup of I^{131} (11), which is such a constant finding that it can be used in the diagnosis, especially to distinguish the stony hard swelling of thyroiditis from cancer, in which the pickup is normal (11). The paradoxical finding of an elevated basal metabolic rate and a low pickup can be explained by assuming that the disease drives out the preformed thyroxin from the gland, producing a temporary hyperthyroidism.

Toxic nodular goiter

In this group of 23 patients the findings were most irregular. The pickup varied from 11 to 90 per cent, the average being 51 per cent (Table 7).

TABLE 6. DISTRIBUTION OF TRACER DOSE OF I^{131} IN 6 CASES OF ACUTE THYROIDITIS

Thyroid pickup, %	Urinary output, %	Plasma		
		Total I^{131}, μc./L.	PBI^{131}, μc./L.	Conversion ratio
2	92	.33	.05	.15
3	65	.33	.02	.07
10	68	.17	.02	.12
1	74	.28	.02	.07
8	51			
4	92			

Some of those with the lowest pickup had the disease in its most advanced form. Practically all of these patients were so ill that operation was considered inadvisable. In none of them was the diagnosis of hyperthyroidism in doubt but since only 1 patient came to operation, it cannot be said that some of them did not have a diffusely hyperplastic thyroid with or without accompanying nodules.

The urinary output of I^{131} varied from 3 per cent to 50 per cent. Blood radioiodine determinations were performed in 8 cases. The results were quite irregular. The conversion ratios were spread as follows: .01, .06, .08, .3, .3, .4, .5, .59.

Werner (11) reported the thyroid pickup of I^{131} in 7 toxic nodular goiters to be little lower than in the toxic diffuse goiters. Shipley *et al.* (2) found little difference in retention. Our findings indicate that the tracer dose behaves in a different manner in toxic nodular goiter and, as a diagnostic

TABLE 7. THE THYROID PICKUP IN TOXIC NODULAR GOITER

Per cent of pickup	Number of patients
11	1
20–29	3
30–39	2
40–49	4
50–59	5
60–69	5
78	1
80	1
90	1

Mean— 51 per cent.
Median—57 per cent.

test, is of much less value than in toxic diffuse goiter. All of our patients with frank exophthalmic goiter had high pickups but we had several patients with severe hyperthyroidism from toxic nodular goiter who had normal pickups.

Hypothyroidism.

We had many patients with a low thyroid pickup and a high urinary excretion of I^{131} who seemed quite normal. We had several patients with true hypothyroidism, in all of whom the pickup was below 15 per cent. Our observations in hypothyroidism are not accurate enough for the drawing of conclusions. It would seem, however, that a patient with hypothyroidism always has a low pickup and a high excretion, but a low pickup and high excretion may occur normally and do not always mean hypothyroidism.

DISCUSSION

In the diagnosis of primary exophthalmic goiter, the findings following a tracer dose of I^{131} are probably more accurate criteria than the basal metabolic rate but they do not indicate the severity of the disease. Because nervousness does not influence the results, a tracer dose is especially useful in a patient who has no enlargement of the thyroid gland and who has borderline symptoms or a borderline basal metabolic rate or in a patient who becomes exceedingly nervous while taking the basal metabolism test. A diagnosis of exophthalmic goiter can be made in most instances without either a tracer dose of I^{131} or a basal metabolic rate. In only a small percentage of patients would the tracer dose actually be useful for diagnosis, although it is always necessary before treatment with I^{131}.

In recurrent postoperative exophthalmic goiter the findings are less accurate but probably are on a par with the basal metabolic rate (Table 8).

TABLE 8. THE TRACER DOSE OF I^{131} IN THYROID DISEASE. SUMMARY

	Thyroid pickup, %	Urinary output, %	Plasma		
			Total I^{131}, μc./L.	PBI^{131}, μc./L.	Conversion ratio
Euthyroid	29	50	.19	.03	.13
Exophthalmic goiter	75	16	.29	.11	.70
Recurrent exoph. goiter	59	27	.21*	.12*	.57*
Toxic nodular goiter	51	29	.27*	.07*	.28*

* Insufficient observations to be of statistical significance.

In toxic nodular goiter, however, the tracer dose may be definitely misleading. The results vary by too wide a margin to be relied upon. Thus, for the diagnosis of hyperthyroidism in a patient with a nodular goiter the tracer dose is inferior to the basal metabolic rate. For this reason, for the diagnosis of all types of hyperthyroidism, the basal metabolic rate is probably the preferable test. For the diagnosis of hypothyroidism we recommend the basal metabolic rate.

In acute thyroiditis the finding of a low pickup may be quite helpful, especially in ruling out cancer. We have not found the tracer dose of any benefit in diagnosing cancer or in localizing intrathoracic goiter, but we have not used well collimated Geiger-Mueller counters.

Of the methods we used, the thyroid pickup was slightly superior to urinary output. This was very likely due to errors in the collection of urine. Either method will suffice in most instances.

The plasma I^{131} is of no diagnostic importance. The PBI^{131} may be used as a single diagnostic test with reasonable accuracy, but we found it to be more erratic than the conversion ratio. In our hands the conversion ratio is the most accurate single determination but it is not sufficiently superior to warrant the extra effort in carrying out the procedures, so we reserve it for the borderline cases.

SUMMARY

1. The diagnostic value of a tracer dose of 50 microcuries of I^{131} has been evaluated with relation to 1) the 24-hour thyroid pickup; 2) the 24-hour urinary excretion; 3) the total plasma I^{131}; 4) the protein-bound plasma I^{131}; and 5) the ratio of PBI^{131} to total I^{131} in plasma (conversion ratio).

2. The thyroid pickup and/or the urinary output of I^{131} were excellent diagnostic criteria in toxic diffuse goiter, less so in recurrent exophthalmic goiter, and of little value in pure toxic nodular goiter.

3. The total plasma I^{131} in itself was of no value in diagnosis. The level of protein-bound I^{131} of plasma is high enough in the hyperthyroidism of toxic diffuse goiter to be diagnostic, but is not as reliable as the conversion ratio.

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NODULAR GOITER AND MALIGNANT LESIONS OF THE THYROID GLAND*

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THE lack of agreement in recent reports concerning the incidence of carcinoma in cases of nodular goiter and the current tendency to minimize the incidence of malignant change in multiple nodular goiter led us to review the association of cancer and nodular goiter in cases observed at the Mayo Clinic. All cases of malignant lesions of the thyroid gland seen at the clinic from 1907 to 1937, inclusive, have been reviewed previously and reported by one of us (Pemberton (1)). The present study, consequently, was limited to cases of malignant lesions of the thyroid gland seen during the decade from 1938 to 1947, inclusive. The findings, in general, with the exception of an unexplained change in the incidence of the different types of carcinoma, were in keeping with those in the earlier series. The findings also supported the belief long held by us and by others, that clinically unrecognizable carcinoma occurs sufficiently often in nodular goiter to warrant thyroidectomy in the great majority of such cases.

During the decade 1938 to 1947, inclusive, a clinical or pathologic diagnosis of malignant lesion of the thyroid gland was made in 360 cases. In 284 cases, the diagnosis was verified histologically, and these only have been considered in the study. The lesion in 76 cases was considered inoperable on clinical examination, or the diagnosis was established by microscopic study of tissue removed elsewhere, and no further treatment was thought indicated at the clinic. In 121 (33.6 per cent) of the entire series of 360 cases, the lesion was considered inoperable on clinical examination or at the time of an exploratory operation. The pathologic classification of malignant lesions of the thyroid gland used for many years at the clinic has been adhered to, and will not be discussed further at this time. With the advent of radioiodine and the increase in knowledge of the function of carcinoma of the thyroid in relation to its histologic structure, there

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well may be reason to introduce certain changes in the classification in the future.

We have had the impression during recent years that papillary lesions were being seen relatively more frequently than in the past, and that both malignant adenomas and diffuse adenocarcinomas were becoming less common. This impression was strongly verified. In the former series, papillary lesions were found in 30 per cent of the cases, whereas in the more recent series the proportion of such lesions had more than doubled (Table 1). The incidence of malignant adenomas decreased from 38 per

TABLE 1. MALIGNANT LESIONS OF THYROID GLAND OBSERVED, 1907 TO 1947, INCLUSIVE

Type of malignant lesion	Cases			
	1907 to 1937*		1938 to 1947	
	Number	Per cent	Number	Per cent
Papillary carcinoma	155	30.0	174	61.3
Carcinoma in an adenoma	197	38.0	52	18.3
Diffuse adenocarcinoma	157	30.4	50	17.6
Epithelioma	4	0.8	3	1.1
Sarcoma	4	0.8	5	1.7
Total	517	100.0	284	100.0

* Reported by Pemberton (1).

cent to 18.3 per cent and that of diffuse adenocarcinomas from 30.4 per cent to 17.6 per cent. The explanation for these changes is not apparent. Differences in pathologic interpretation over the years, particularly in the group of malignant adenomas, may be a factor, as may be the fact that proportionately fewer adenomatous goiters are being seen at present than in the past. In both series, the pathologic diagnosis of epithelioma or of sarcoma was made rarely.

The findings with respect to age re-emphasize the fact that carcinoma of the thyroid may occur in young persons. In approximately 15 per cent of cases of papillary adenocarcinoma, the patients were less than 20 years of age, and in more than 30 per cent they were less than 30. Such lesions are by no means limited to children and young adults, however (Fig. 1). In 36 per cent of the cases the patients were 50 years of age or older. The average age of patients was as follows: 41.9 years in cases of papillary adenocarcinoma, 46 years in cases of adenocarcinoma in an adenoma, 54.8 years in cases of diffuse adenocarcinoma, and 45.5 years in all cases

of malignant lesions of the thyroid gland. Sixty-five per cent of the patients in the present series were females, and 35 per cent were males, which is in keeping with the usually reported ratio of approximately 2:1.

SOLITARY NODULE OF THE THYROID AND CARCINOMA

Cole and his colleagues (2, 3), Lahey and Hare (4) and Cope and associates (5) recently have emphasized the high incidence of carcinoma in cases in which a single nodule, as distinguished from multiple nodules, was palpable in the thyroid. An attempt was made to investigate this as-

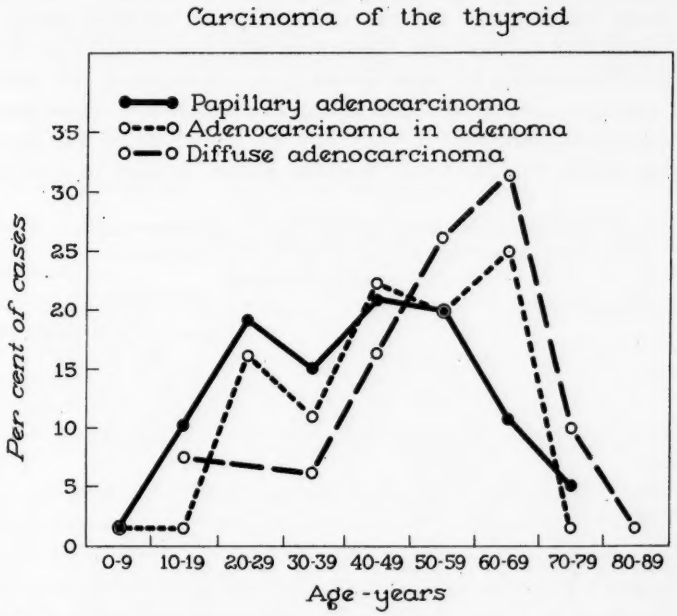

FIG. 1. Incidence of carcinoma of thyroid gland according to age of patients.

pect of the problem in the present series of cases. It soon became evident that, judging from the records, there was little agreement among physicians who had examined the patient as to whether there was a single mass or multiple nodules within the thyroid gland. There was, in addition, little agreement between the clinical findings and the pathologist's report. In cases in which several examiners agreed that the nodule was single, examination of the surgical specimen, more usually than not, revealed multiple adenomas. In our experience, a truly solitary nodule is rather unusual, as are cases in which the pathologic changes are limited to one region of the thyroid. We agree that carcinoma is more likely to be found

in cases in which the pathologic changes in the thyroid gland are limited to one region. However, we were unable, from the study of our records, to find the proportion of solitary nodules which proved malignant on pathologic examination. Cope, Dobyns, Hamlin and Hopkirk (5), in a consecutive series of cases in which the pathologic changes were localized, found that the incidence of malignant lesions was 19 per cent. This incidence was approximately double that found for all nodular goiters in their series of cases.

NODULAR GOITER AND CARCINOMA

The gross incidence of carcinoma in cases of nodular goiter in the present series was 4.8 per cent. The figure is identical with that found by one of us (Pemberton) in cases observed at the clinic in the years 1907 to 1937 inclusive. The proportion of cases in which carcinoma was found varied somewhat from year to year, but, on the whole, it was reasonably consistent (Table 2). The term "nodular goiter" is used in this paper to

TABLE 2. INCIDENCE OF CARCINOMA OF THYROID GLAND IN CASES IN WHICH OPERATION FOR NODULAR GOITER WAS PERFORMED, 1938 TO 1947, INCLUSIVE

Year	Cases of nodular goiter	Cases in which carcinoma was present	
		Number	Per cent
1938	511	26	5.1
1939	559	26	4.7
1940	486	26	5.3
1941	501	22	4.4
1942	552	21	3.8
1943	596	31	5.2
1944	645	25	3.9
1945	628	28	4.5
1946	655	31	4.7
1947	546	34	6.2
Total	5,679	270	4.8

designate all thyroid lesions, including clinically evident carcinoma, which were found to be nodular on clinical examination. The figure is quite meaningless as a measure of the danger with respect to the development of cancer in a nodular goiter, since clinical acumen extends far beyond the mere palpation of nodules. The figure is of some interest, however, because it is in such close agreement with the incidence of carcinoma in

cases of nodular goiter as reported by Brenizer and McKnight (6) (4 per cent), Horn, Welty, Brooks, Rhoads and Pendergrass (7) (6.3 per cent), Crile (8) (5.6 per cent), and Ward (9) (4.8 per cent).

CARCINOMA AND ADENOMATOUS GOITER WITHOUT HYPERTHYROIDISM

During the decade covered in this review, thyroidectomy was carried out because of adenomatous goiter without hyperthyroidism in 3,247 cases. A carcinoma was found in the resected tissue in 244 (7.5 per cent) of the 3,247 cases. This incidence, although in keeping with that reported by many other authors, is misleading in that the clinical impression as to

TABLE 3. INCIDENCE OF CARCINOMA OF THYROID GLAND IN CASES IN WHICH OPERATION FOR EXOPHTHALMIC GOITER OR ADENOMATOUS GOITER WAS PERFORMED, 1938 TO 1947, INCLUSIVE

Clinical diagnosis	Cases	Cases in which carcinoma was present	
		Number	Per cent
Exophthalmic goiter	3,029	14	0.5
Carcinoma not suspected	3,027	13	0.4
Adenomatous goiter			
With hyperthyroidism	2,229	26	1.2
Carcinoma not suspected	2,222	19	0.9
Without hyperthyroidism	3,247	244	7.5
Carcinoma not suspected	3,121	118	3.8

the possibility of carcinoma was not considered. In 126 of the 244 cases in which the presence of carcinoma was proved by pathologic examination, there was some indication in the history that carcinoma was suspected on clinical examination. Cases were placed in this category if any examiner used such a phrase as "the nodule is unusually firm," or a certain nodule "has been increasing in size," or "the findings suggest the possibility of carcinoma," and so forth. It was assumed, almost certainly fallaciously, that, unless some such comment was made, the presence of carcinoma was not suspected. In 3,121 of the 3,247 cases of adenomatous goiter without hyperthyroidism, there was no indication in the records that carcinoma was suspected. Carcinoma was found in 118 (3.8 per cent) of the 3,121 cases. We regard this figure as a reasonable estimate of the incidence of carcinoma, unsuspected clinically, in cases of adenomatous goiter without hyperthyroidism.

ADENOMATOUS GOITER WITH HYPERTHYROIDISM AND CARCINOMA

The corresponding figures in cases of adenomatous goiter with hyper-

thyroidism are definitely lower. However, the incidence of carcinoma was found to be materially higher than that reported recently by Lahey and Hare in cases of toxic goiter. A carcinoma was found in 26 (1.2 per cent) of the 2,229 cases in which thyroidectomy was carried out because of adenomatous goiter with hyperthyroidism (Table 3). Carcinoma was suspected clinically in only 7 cases. An unsuspected carcinoma was found in 19 (0.9 per cent) of 2,222 cases. The problem of the incidence of carcinoma in cases of toxic nodular goiter is less important than that in cases of nontoxic goiter, since toxic nodular goiter generally is treated surgically. The occurrence of unsuspected carcinoma in 1.0 per cent of cases should be considered, however, in cases in which nodular goiter is treated by methods other than resection.

TABLE 4. DURATION OF GOITER PRIOR TO DIAGNOSIS OF CARCINOMA IN 213 CASES

Duration of goiter	Type of carcinoma			Cases	
	Papillary adeno-carcinoma	Adeno-carcinoma in adenoma	Diffuse adeno-carcinoma	Number	Per cent
Less than 7 mo.	31	11	13	55	25.8
7 to 11 mo.	19	1	6	26	12.2
1 to 4 yr.	33	14	6	53	24.9
5 to 9 yr.	18	8	3	29	13.6
10 to 19 yr.	14	6	6	26	12.2
More than 19 yrs.	13	6	5	24	11.3
Total	128	46	39	213	100.0

EXOPHTHALMIC GOITER AND CARCINOMA

In keeping with previous reports from the clinic, carcinoma was found rarely in cases of exophthalmic goiter. It occurred in 14 (0.5 per cent) of 3,029 cases in which exophthalmic goiter was treated surgically (Table 3). Two of us (Pemberton and Black (10)) previously reported that the lesions are almost invariably small sclerosing papillary growths which neither tend to recur nor to metastasize. The rarity and the character of such lesions in cases of exophthalmic goiter suggest that carcinoma need not be seriously considered in such cases.

DURATION OF GOITER

Little could be inferred concerning the possibility of cancer from the duration of the goiter. Data on this point were available in 213 cases (Table 4). In a fourth of the cases, a goiter had been present for six months or less; in more than a third of the cases it had been present for one year or less. In such instances the relatively recent development of a goiter obviously should have aroused suspicion of the possibility of a malignant lesion. However, in approximately 40 per cent of the cases, a goiter had been present for five or more years before the thyroidectomy was performed. Similarly, the history of an increase in size of the goiter was inconstant in cases of malignant lesions. In only 27 per cent of cases was there any evidence in the record that the goiter had recently changed in any way. It probably can be inferred that in many cases of cancer of the thyroid there is no evident change in the goiter which would suggest the diagnosis.

SIZE OF THE GOITER

As was anticipated, there was no relationship between the size of the surgical specimen and the type of carcinoma (Table 5). The papillary

TABLE 5. WEIGHT OF SURGICAL SPECIMEN AND TYPE OF CARCINOMA IN 128 CASES

Weight, Gm.	Type of carcinoma			Cases	
	Papillary adeno-carcinoma	Adeno-carcinoma in adenoma	Diffuse adeno-carcinoma	Number	Per cent
Less than 30	52	9	2	63	49.2
30 to 60	22	4	2	28	21.8
More than 60	13	16	8	37	29.0
Total	87	29	12	128	100.0

lesions usually occurred in small goiters, whereas in other types of carcinoma the goiters tended to be larger. However, large goiters did not preclude papillary lesions, nor small glands, other types of malignant lesions.

PREOPERATIVE CLINICAL DIAGNOSIS AND CARCINOMA

In 123 (44.5 per cent) of the 276 cases of carcinoma the clinical diagnosis was benign goiter (Table 6). Conversely, in 55 per cent of cases the pres-

ence of carcinoma was suspected, or enlarged cervical lymph nodes, which would warrant biopsy, were present. The presence of a carcinoma was suspected on clinical examination in 72 of the 174 cases of papillary adenocarcinoma and cervical lymphadenopathy was present in an additional 22 cases. Thus in 55 per cent of the 174 cases, operation was indicated on the basis of the clinical evidence. The corresponding figure for the malignant adenomas was less than 35 per cent, whereas that for the diffuse adenocarcinomas was 80 per cent. In general, it may be said that approximately

TABLE 6. CLINICAL DIAGNOSIS IN 276 CASES OF CARCINOMA OF THYROID GLAND

Clinical diagnosis	Type of carcinoma*			Cases	
	Papillary adenocarcinoma	Adenocarcinoma in adenoma	Diffuse adenocarcinoma	Number	Per cent
Cervical lymphadenopathy	22	1	2	25	9.1
Benign goiter	80	34	9	123	44.5
Carcinoma questionable	30	8	12	50	18.1
Carcinoma	42	9	27	78	28.3
Total	174	52	50	276	100.0

* As disclosed by examination of surgical specimen.

50 per cent of papillary lesions, 65 per cent of malignant adenomas, and 20 per cent of diffuse adenocarcinomas were not associated with clinical findings suggestive of carcinoma. These findings do not imply that thyroidectomy was advised solely because of the possibility of carcinoma in those cases in which the preoperative diagnosis of benign goiter was made. In the majority of such cases, the goiter was removed because of its size, because of the presence of toxemia, or for other reasons. However, the question of carcinoma probably had some influence in helping to make the decision to advise thyroidectomy in virtually every case in the series.

SUMMARY

The malignant lesions of the thyroid gland seen at the Mayo Clinic from 1938 to 1947, inclusive, differed from those seen prior to 1938 in that the incidence of papillary adenocarcinoma increased from 30 to 60 per cent, that of carcinoma in an adenoma decreased by more than half, and that of diffuse adenocarcinoma decreased by more than a third.

Carcinoma was found in 4.8 per cent of a series of more than 5,500 cases in which a nodular goiter was treated surgically. It was found in 7.5 per cent of more than 3,000 cases in which thyroidectomy was performed because of adenomatous goiter without hyperthyroidism. A carcinoma, unsuspected on clinical examination, was found in 3.8 per cent of the cases.

Carcinoma was found in approximately 1.0 per cent of more than 2,000 cases of adenomatous goiter with hyperthyroidism, and in 0.5 per cent of 3,000 cases of exophthalmic goiter.

In the series of 276 cases of carcinoma, approximately half of the papillary lesions, two thirds of the malignant adenomas, and a fifth of the diffuse adenocarcinomas were not suspected on clinical examination.

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CARCINOMA OF THE THYROID GLAND IN YOUTH*

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OUR attention was forcibly directed to the problem of thyroid cancer in young individuals by the recent simultaneous observation of 3 "teen-agers" with this disease, 1 of whom gave a history of a lateral cervical mass which had been under a physician's observation for a period of nine years. Although in 1935 Kennedy (1) could collect but 6 cases from the American medical literature of the preceding twenty years, reports since then have been more numerous and several authors have placed especial emphasis on the occurrence of thyroid cancer in youthful patients (2–6). Duffy and Fitzgerald (7) have recently published an excellent review of 28 cases in patients 18 years of age or less, from the Memorial Hospital. The 28 cases in this age group represented 6.5 per cent of a total of 430 thyroid carcinomas. For the most part, previous papers have dealt with the disease in children, each author setting his own upper age limit of childhood. Our study is concerned with patients 25 years of age or younger at the time the diagnosis of thyroid carcinoma was made. We have arbitrarily limited our group for three reasons: first, because we have encountered approximately as many thyroid cancers in the first half of the third decade as in the entire first two decades of life; second, the clinical and pathologic manifestations of the disease in patients in their early twenties appear very similar to those seen in younger patients; and, third, patients first treated when they are 20 to 25 years of age frequently give a history of having had the initial manifestations of the disease in childhood.

INCIDENCE

We have operated on a total of 22 patients, 25 years of age or younger, with carcinoma of the thyroid gland. This represents 13.8 per cent of 159 thyroid carcinomas observed in this hospital among a total of 3,328

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surgical goiters over a period of seventeen and a half years. The clinical and pathologic data regarding these patients are summarized in Table 1. Several additional cases have been excluded, in which the thyroid was considered suspicious on histologic examination but could not be definitely diagnosed as carcinomatous.

Nineteen of these 22 patients were encountered in the past six years (January 1, 1945 to December 31, 1950). During this same period of time a total of 62 thyroid lesions (exclusive of toxic diffuse goiters) removed from patients 25 years of age or less were studied in the Laboratory of Surgical Pathology. A breakdown of the classifications of these surgical thyroid lesions according to age is presented in Table 2.

This incidence of carcinoma of 30.6 per cent among surgical goiters (exclusive of toxic diffuse goiters) from patients up to 25 years of age is to be compared with an incidence of carcinoma of 5.5 per cent for all age groups in this hospital from 1933 to 1945 (8), and a corresponding figure of 9.2 per cent for the past six years. Although we have not diagnosed thyroid carcinoma in patients under 12 years of age, it is of interest that, beginning with the second decade of life, the incidence of carcinoma among surgical goiters decreases with age. During this same recent six-year period, we have encountered 8 patients between the ages of 26 and 30 with thyroid carcinoma, among 54 patients with surgical goiters (excluding toxic diffuse goiters). This incidence of 14.8 per cent continues the downward trend of cancer incidence with increasing age. Comparable incidences have been reported by Ward (6) who found 4 carcinomas in 10 nodular goiters (40 per cent) in patients under 15 years of age but only 10 carcinomas in 58 nodular goiters (17.2 per cent) in patients under 20 years of age. Dailey and Lindsay (2) found that 59 per cent of the nontoxic nodular goiters they observed in patients less than 20 years old were malignant. These figures give strong emphasis to Kennedy's (1) statement that any mass in the thyroid glands of children should be suspected of having malignant qualities.

ETIOLOGIC FACTORS (AGE, SEX, ENDOCRINE FACTORS)

The incidence of carcinoma of the thyroid with relation to age has just been discussed. The ages of the patients in this series at the time the diagnosis of carcinoma was made contrast sharply, however, with their ages at the time of the first observation of a lateral cervical or thyroid mass (Table 3). The frequent occurrence of long time intervals between onset and diagnosis is striking (nine to twelve years in 6 patients). In their study of 28 instances of thyroid carcinoma in patients under 18 years of age, Duffy and Fitzgerald (7) observed a peak incidence of onset between the ages of 10 and 15, slightly earlier in girls, and believed that

TABLE 1

Case No.	Sex	Age at time of onset (yrs.)	Age at time of diagnosis (yrs.)	Goiter	"Lateral aberrant thyroid syndrome"	Size of primary tumor (cm.)	Invasion	Blood vessel invasion	Histologic type	Metastases		Treatment					Survival (years)		Remarks
										Cervical lymph nodes	Other	Thyroidectomy*	Neck dissection	X-ray	I^{131}	I^{131} uptake	From time of onset	From time of diagnosis	
1	M	3	15	+	+	2 Nodules 6×5×2	+	+	Adenomatous	Bilateral	Lungs	P			+	+	15	3	Stationary mass in neck. Lung lesions regressed.
2	M	12	17	0	+	2.5×2×2	+		Adenomatous	+		L	+				11	6	No clinical evidence of disease.
3	F	18	18	0†	+	2	+		Adenomatous, papillary, solitary, squamous	+		L	+	+			4	4	Left country and lost to follow-up two years ago.
4	M	20	22	0	+	0.7	+	+	Papillary	+		L	+	+			9	7	No clinical evidence of disease.
5	M	10	19	0	+	No thyroidectomy			Papillary	+			+	+			17	8	Complaining of back pain. Results of clinical studies negative.
6	M	3	12	+		1.8×2×1.4	+	+	Adenomatous	+ (clin.)		P		+	+	+	13	4	No clinical evidence of disease.
7	M	20	20	+	+	4 Nodules 1.5–4.5	+	+	Adenomatous & papillary	+		L	+	+		0	2	2	No clinical evidence of disease.
8	F	‡	25	0	+	2×1×1	+		Papillary	+		L	+	+			‡	2	No clinical evidence of disease. Enlargement of nodes first noticed during pregnancy, terminated by delivery three months before diagnosis.
9	F	23	24	+		1	+	+	Papillary			L		+			2	1	No clinical evidence of disease.
10	M	14	19	+		4×2×1.5	+		1—small cell 2—large spindle			P		+			21	16	No clinical evidence of disease. Large spindle cell carcinoma resected one year before, fifteen years after original diagnosis.
11	F	22	22	+	+	4×1.5×1	+		Papillary	+	Lungs	P			+	+	1	1	No change.

12	F	24	24	+		"Pea"	+		Papillary	+		L	+	+			½	½	No clinical evidence of disease.
13	M	20	23	+	+	6×6.5×8	+		Adenomatous & solid	Bilateral		T					4	1	No clinical evidence of disease.
14	M	21	23	+	+	Large	+	+	Large spindle cell, with some differentiation	+		B		+		0	4½	2½	Under I^{121} treatment elsewhere. Disease regressing.
15	F	9	17	0	+	2.5×2×1	+		Papillary	+		L	+	+			11	3	Recently treated for local recurrence in neck.
16	M	10	13	+	+	3	+	+	Adenomatous & solid	+		L	+	+			7	4	No clinical evidence of disease. Malignant adenoma resected one wk. before lobectomy and neck dissection.
17	M	12	13	+	+	4.8×3.2×2.4	+		Adenomatous	+		L	+	+			3	1½	No clinical evidence of disease.
18	F	18	18	+		2 Nodules each 2.5×2×1.5	+	+	Adenomatous & papillary			L	+						Recent prophylactic neck dissection. No metastases found.
19	F	22	22	+		Lobectomy elsewhere			Adenomatous	+		T	+			+			First noted in second trimester of pregnancy. Recently treated.
20	M	9	18	+	+	2 Nodules 2.5×1.5 & 4×3	+		Adenomatous	+		T	+				9		Recently treated.
21	F	18	18	+		3.3	+	+	Adenomatous			L		+					Recently treated.
22	F	23	24	+		4	+	+	Adenomatous, papillary, solid			L		+			2	1	No clinical evidence of disease.

* P = Partial.
L = Lobectomy (and removal of isthmus).
T = Total or subtotal.
B = Biopsy.
† Simple nodule removed two years previously.
‡ Nodules "as long as she can remember."

TABLE 2. CLASSIFICATION OF SURGICAL THYROID LESIONS IN YOUTH, ACCORDING TO AGE AT TIME OF DIAGNOSIS

Age (yrs.)	Nontoxic diffuse goiter	Nontoxic nodular goiter	Toxic nodular goiter	Adenoma	Thyroiditis	Carcinoma	Total	Per cent carcinomatous
0–5		1					1	—
6–10				1*			1	—
11–15		2				4	6	66.7
16–20		5	4	2		7	18	38.8
21–25	4	16	1	4	3	8	36	22.2
Totals	4	24	5	7	3	19	62	30.6

* This patient's adenoma occurred in association with nontoxic multinodular goiter.

this indicated a correlation with puberty. We, however, have observed more instances of known onset after the age of 15 than before. In our series we have noted no familial histories of thyroid disease; nor a history of previous radiation therapy for thymic enlargement, as was the case in 10 of Duffy's and Fitzgerald's patients.

The great preponderance of thyroid disease in general in the female, and the somewhat less marked but still distinct preponderance of thyroid carcinoma in this sex are well known. It is striking, then, that the 22 thyroid carcinomas in our patients 25 years of age or under were equally divided between the sexes; but only 3 of 43 non-malignant goiters observed in this series in patients under 26 years of age occurred in males. This means that 11 of 14 nodular thyroid lesions in males in this age group were malignant. Duffy and Fitzgerald's series showed only a slight predilection for females but other authors (2, 3, 5) observed the same predominance of thyroid carcinoma in female children as in adults. The significance of these observations is not at all clear but the sex distribution of thyroid

TABLE 3. CARCINOMA OF THE THYROID IN YOUTH. DISTRIBUTION ACCORDING TO AGES AT ONSET AND AT TIME OF DIAGNOSIS

Age (yrs.)	At time of	
	Onset	Diagnosis
0– 5	2*	—
6–10	4	—
11–15	3	4
16–20	6	9
21–25	6	9
Totals	21*	22

* One patient had "nodules as long as she could remember."

cancer in childhood and youth, taken together with Duffy and Fitzgerald's correlation of onset of symptoms with the age of puberty and the onset of one of our tumors (Case 19) and the acceleration of another (Case 8) during pregnancy suggest that some complex endocrine influence may be operating in at least some cases of thyroid carcinoma.

CLINICAL SYMPTOMS

Fourteen of the 22 patients in this series had what we might term the "lateral aberrant thyroid syndrome"—that is, their initial complaint was a lateral cervical mass ultimately proven, in 13 cases, to be carcinoma of thyroid origin. In 2 of these patients primary carcinomas in the thyroid gland proper were palpable upon the admission examination, although the patients had been unaware of goiters. In 6 patients goiters developed in the interval, varying from one to twelve years, between onset of the lateral mass and referral to the hospital for treatment. Of the remaining 6 patients without palpable goiters, 2 were found to have tumors at operation and 3 presented no operative findings suggestive of carcinoma, although carcinomas were readily found on pathologic examination. The remaining patient (Case 5), the only one in this group without proven carcinoma in the main thyroid gland, has never had a thyroidectomy. He has survived eight years since the performance of a neck dissection and seventeen years since the onset of his lateral cervical tumor. This experience leads us to agree wholeheartedly with those who have emphasized that the so-called "lateral aberrant thyroid syndrome" actually represents cervical lymph node metastasis from occult carcinoma of the thyroid gland (9). It is worthy of note, however, that this "syndrome" is largely one of the younger age groups (10) and commonly pursues a distinct, protracted clinical course.

Among the 5 patients with lymph node metastases and without palpable goiters, the primary carcinomas varied from 0.7 cm. in diameter to $2.5 \times 2 \times 2$ cm. Those detected at operation (Cases 8 and 15) were no larger than those first noted in the laboratory (Cases 2, 3 and 4). On the other hand, 2 patients with clinical goiters (Cases 9 and 12) had 1-cm. and "pea-sized" tumors, respectively. Such discrepancy between the size and palpability of thyroid nodules serves to point up, first of all, the importance of careful physical examination of the neck and, secondly, the necessity of pathologic diagnosis of lateral cervical masses.

Case 3 deserves special mention. The patient, a female, had a simple involutional nodule of the thyroid resected in this institution in 1942, when she was 16 years of age. Two years later a lateral cervical mass developed and she was promptly referred to the hospital. There was no palpable goiter. The lateral cervical mass was removed for pathologic

examination and, although its thyroid origin was readily apparent, it was difficult to identify it as malignant because of its excellent differentiation (Fig. 1-A). Nevertheless, radical neck dissection and hemithyroidectomy were carried out. There were multiple lymph node metastases, which were as well differentiated as the original node biopsy specimen and also a less well differentiated, frankly invasive carcinoma in the homolateral thyroid lobe, which measured 2 cm. in its greatest dimension (Fig. 1-B). The patient was free of any demonstrable evidence of disease four years later, at which time she moved out of this country. In Case 2, the patient was a 17-year-old boy, who presented an identical diagnostic problem and similar subsequent surgical and pathologic findings.

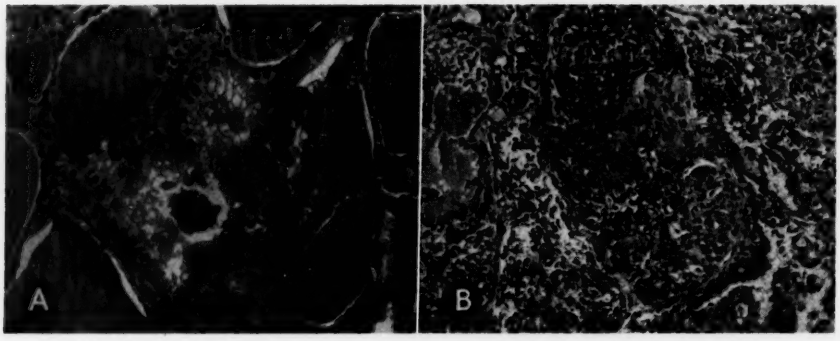

FIG. 1. *Case 3.* A. Well-differentiated lateral cervical lymph node metastasis. B. Invasive primary carcinoma of thyroid gland, showing epidermoid differentiation.

Of this group of 14 patients presenting the "lateral aberrant thyroid syndrome," 8 were first admitted to the hospital because of the lateral cervical mass or masses, and 5 for this complaint plus thyroid enlargement. The fourteenth patient (Case 1) was a 15-year-old boy who, twelve years before, had had a lateral cervical mass removed elsewhere and diagnosed as "lateral aberrant thyroid." He was admitted to the medical service of this hospital for study of widespread pulmonary disease detected on routine roentgenography. He also had a large goiter and cervical lymph node metastases. Following partial thyroidectomy with removal of some of the cervical lymph nodes, he was treated with radioactive iodine. The lung lesions have regressed under this therapy (Fig. 2) and at present, three years since his first admission here, his only clinical evidence of disease is a hard node in the left lateral cervical region which does not appear to be enlarging.

The remaining 8 patients in this series were referred for treatment

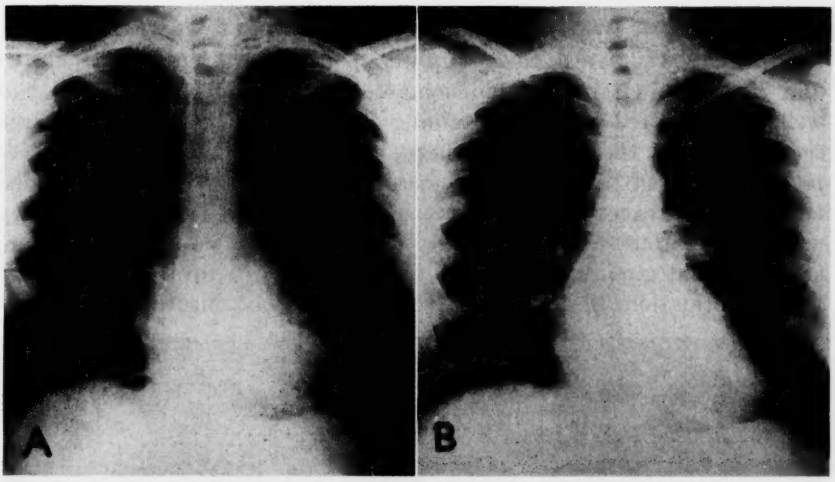

FIG. 2. *Case 1.* A. Roentgenogram showing extensive pulmonary metastases at time of admission.

B. Roentgenogram made approximately two years later, demonstrating marked clearing after radioactive iodine treatment.

because of nodules in the thyroid gland. Our experience with the clinical manifestations of thyroid carcinoma in youth is very similar to that of Duffy and Fitzgerald (7), although a higher proportion of our patients had a thyroid nodule as the presenting complaint. This difference may be due to the fact that our group includes a number of patients between the ages of 18 and 25, whereas they limited their series to patients under 19 years of age.

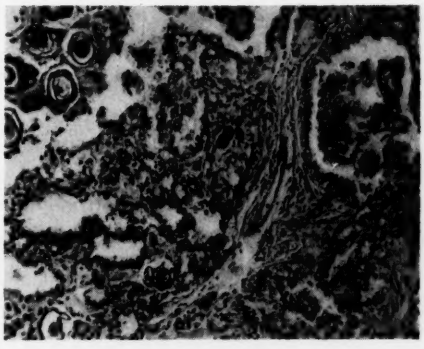

FIG. 3. *Case 12.* Papillary carcinoma of thyroid. Neck dissection was performed but lymph node metastases were not found.

PATHOLOGY

Seven of the tumors in this group were predominantly papillary (Fig. 3) and 7 we have classified as adenomatous. The latter were composed of well differentiated, colloid-containing follicles but the relatively large size of the cells, their clear cytoplasm, and the irregularity of the follicles readily identified them as carcinomas (Fig. 4-A). It is to be emphasized that, with rare exceptions, the tumors were not of pure type, and papillary and adenomatous areas were freely intermixed (Fig. 4-B). In addition, areas of solid growth in cords or alveolus-like structures without good follicle formation were frequently observed. Classification was made

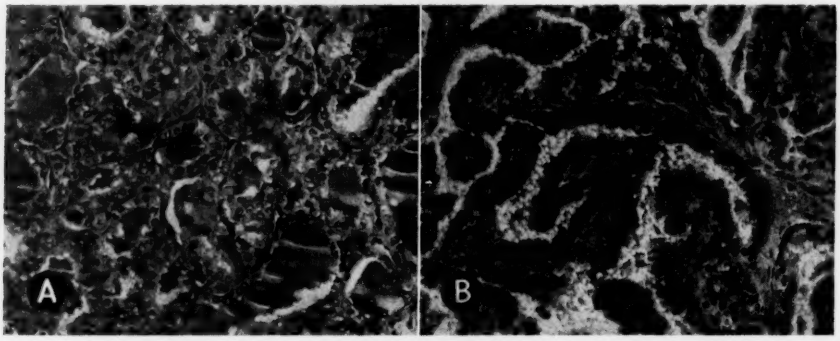

FIG. 4. *Case 20.* A. Predominantly adenomatous carcinoma of thyroid. There were extensive lymph node metastases.

B. One of several papillary areas in this tumor.

according to the predominant tumor type. In 6 tumors no single histologic pattern could be considered predominant. Four of these were more or less equally papillary and adenomatous and 2 more or less equally adenomatous and solid. One of these mixed tumors also showed areas of epidermoid differentiation (Case 3) (Fig. 1-B). The remaining 2 tumors were solid. In Case 10 a minute, compact, small-cell carcinoma was found in a large multinodular goiter sixteen years before, when the patient was 19 years of age. A recurrent, or new, tumor was resected one year previously and was composed of large fusiform cells grouped in compact masses or cords with little differentiation. This tumor type was also present in Case 14 (Fig. 5) and is described in detail elsewhere (11) (Table 4).

In Case 14 an inoperable, poorly differentiated, solid carcinoma responded poorly to radiation therapy and led us to anticipate an early fatal outcome. However, the disease was advanced when first observed by us and recently there has been a favorable response to radioactive iodine administered elsewhere. With this questionable exception, histo-

pathologic typing in this series does not appear to have a significant relationship to the clinical manifestations of the disease. Cervical lymph node metastasis occurred as frequently with one type of tumor as with another; and of the 2 patients with pulmonary metastasis, one had a well differentiated adenomatous tumor, the other a papillary carcinoma. This is in general agreement with Duffy and Fitzgerald's (7) report, although a

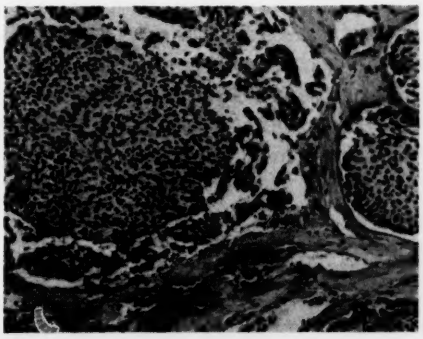

FIG. 5. *Case 14.* Solid, spindle-celled carcinoma of thyroid. This patient has extensive local disease, responding slowly to treatment with radioactive iodine.

higher proportion of their tumors were predominantly papillary. They regard the solid carcinomas as being associated with the poorest prognosis. It does seem significant, however, that in the younger age groups, thyroid carcinoma is almost always of the papillary or adenomatous types and that the less well differentiated and more malignant tumors are rarely encountered.

In the 20 cases in which we have been able to examine the primary tumor (in Case 5 thyroidectomy was not performed, and in Case 19 thyroidectomy was performed elsewhere), all the tumors were locally invasive. Blood vessel invasion was observed in 10 cases, most of which included

TABLE 4. DISTRIBUTION OF HISTOPATHOLOGIC TYPES OF TUMOR

	No. of cases
Predominantly papillary	7
Predominantly adenomatous	7
Mixed papillary and adenomatous	4
Mixed adenomatous and solid	2
Solid	2
Total	22

extensive adenomatous areas. However, 1 tumor was solid and 2 predominantly papillary. Seventeen patients have had cervical lymph node metastases. The metastases were bilateral in 2 patients, both with extensive local tumors crossing the midline. In 1 case, the presence of lymph node metastases was not proven histologically, but seemed unequivocal on clinical grounds (Case 6). On the basis of this experience, we have advised prophylactic neck dissection in 1 patient, but metastasis was not found (Case 18). Pulmonary metastases were observed in 2 patients and, in both, were asymptomatic although widespread. As noted previously, these metastases have regressed in one of the patients (Case 1) under radioactive iodine therapy (Fig. 2). The other patient (Case 11) is being similarly treated but thus far (one year), the appearance of the roentgenogram has not changed.

TREATMENT AND RESULTS

Although these patients have not been treated uniformly, we have evolved a program of management. In those patients presenting the "lateral aberrant thyroid" syndrome, we believe that unilateral radical neck dissection and hemithyroidectomy with removal of the isthmus should be carried out after, of course, biopsy proof of the nature of the disease. We have usually followed this with roentgen therapy. In patients whose presenting complaint is a thyroid nodule, we have carried out hemithyroidectomy with removal of the isthmus followed, at the same or a subsequent sitting, by unilateral neck dissection if there are distinctly enlarged lymph nodes. We are inclined to believe that all patients in this age group should have neck dissections because of the almost regular occurrence of lymph node metastases, but confirmation of this impression must await further experience, since the only patient in whom prophylactic neck dissection was performed was not found to have metastatic disease. Furthermore, many patients in whom neck dissections have been performed for known and sometimes extensive metastases have done well for long periods of time.

Even in patients in whom extensive invasion has made it impossible to remove the tumor completely by surgical means, we have performed partial thyroidectomies, removing as much of the tumor and remaining normal thyroid gland as possible, in the hope of facilitating radioactive iodine therapy.

In the more recent cases of this series we have attempted to carry out radioactive iodine tracer studies whenever the diagnosis of thyroid carcinoma was known or suspected. Such studies have included the preparation of radioautographs of the removed tumors. Of 6 patients studied in this manner, the tumors of 4 have appeared to take up radioactive iodine

in significant amounts. Three of these patients have been treated primarily by this means—2 with pulmonary metastases (Cases 1 and 11) and 1 (Case 6) in whom the entire primary tumor of the thyroid could not be removed because of invasion of the esophagus. As noted, the response to I^{131} therapy in Case 1 has been dramatic, with regression of the pulmonary metastases. In Case 6, the progress of the disease has been arrested and the patient has remained clinically well for four years. In Case 11, the pulmonary lesions have remained static for a year.

Many of our patients have been treated too recently to permit us to speak of end-results, particularly with respect to as slowly progressive a disease as this appears to be. It is significant that all our patients are clinically well and carrying on their accustomed activities in normal fashion. Our longest survival, from the time the diagnosis was made, is sixteen years, but this patient has had a new, or recurrent, tumor treated surgically within the past eighteen months. Three other patients have survived more than five years. Survivals from the time of known onset of the disease range up to twenty-one years with 6 survivals of more than ten years. Other authors have also remarked upon the relatively benign character of thyroid cancer in the younger age groups (1, 2, 4, 7, 12, 13).

SUMMARY

Carcinoma of the thyroid gland is not rare in patients under the age of 26 years. Twenty-two cases from the Surgical Service of the Hospital of the University of Pennsylvania are reviewed. Its incidence (30.6 per cent in this series) relative to the incidence of other forms of surgical thyroid disease (excepting toxic diffuse goiter) is extremely high as contrasted with that in adults.

The incidence of cervical lymph node metastasis in this age-group is very high (77 per cent). In more than half of the patients clinical evidence of metastasis develops before a goiter is apparent—the so-called "lateral aberrant thyroid" syndrome. Cervical lymph node metastases may be present for years before a primary tumor of the thyroid becomes manifest; indeed, at times careful pathologic examination of the gland may be necessary to disclose it. Therefore, it is imperative that all lateral cervical nodes be removed for pathologic examination.

In the present state of our knowledge, we believe that the disease should be treated by thyroidectomy (hemithyroidectomy with removal of the isthmus if the disease is unilateral), neck dissection if there are palpably enlarged cervical lymph nodes, and postoperative roentgen therapy. When the diagnosis of thyroid carcinoma is suspected, we carry out tracer studies with radioactive iodine. Even inoperable tumors should be removed surgically, as completely as possible, together with any remaining normal

thyroid in order to facilitate the possible subsequent use of this drug. Two of the patients in this series have responded exceedingly well to therapy with I^{131}, one showing regression of extensive pulmonary metastases.

Despite the frequent presence of metastases at the time of the first observation, thyroid cancer in youthful patients appears to be a relatively benign and slowly progressing disease. Even in the face of extensive pulmonary metastasis, the outlook is by no means hopeless.

In order to accomplish earlier diagnosis and treatment, thyroid nodules must be resected and biopsy specimens taken from lateral cervical lymph node enlargements promptly after detection, no matter what the age of the patient. However, the younger the patient, the more urgent are these diagnostic procedures.

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RECURRENT AND PERSISTENT HYPERTHYROIDISM*

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THE writer's earliest years in surgical training and practice were during a period when the classic operation for bilateral goiter was a bilateral, partial resection, then improperly labeled "subtotal." Perusal of operative records of such cases regularly reveals such estimates as "two-thirds of one lobe and five-sixths of the other were removed." The inadequate results of such a procedure were late in being evaluated, as in the case of gastro-enterostomy or limited resection of the stomach for duodenal ulcer. That the results were far from ideal was shown by the unwillingness of many internists to use the word "cure" to describe the usual sequelae of partial thyroidectomy.

Surgeons were still unaccountably influenced by Kocher's earlier dictum that postoperative hypothyroidism should be feared and was to be classed as a *complication* of thyroidectomy in the same undesirable category as nerve injury or hypoparathyroidism. This attitude was maintained despite the fact that the ability of desiccated thyroid substance and thyroxine, administered orally, to restore and maintain normal metabolic status had been amply demonstrated in the treatment of spontaneous myxedema.

A study by the writer in 1932 of the cases of persistent or recurrent hyperthyroidism seen during the preceding five years led to the following conclusions and hypotheses:

1. Persistent or recurrent hyperthyroidism represents a technical failure on the part of the operator and is the result of leaving too much toxic goiter *in situ*.

2. The surgeon should fasten his attention upon leaving as little toxic goiter as possible to line a generous portion of lateral capsule for the protection of the extracapsular structures. So little thyroid tissue should be left that is it unable to give rise to clinical symptoms in response to whatever extrathyroid stimulus to hyperplasia persists after thyroidectomy.

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3. After a sufficiently radical subtotal thyroidectomy, the anticipated permanent myxedema should be prevented by early postoperative observation and the administration of thyroid substance or thyroxine in maintenance dosage. The need for such a daily maintenance dose should be life-long.

4. Such a program should give complete assurance against the persistence or recurrence of hyperthyroidism after operation for bilateral goiter, diffuse or nodular, within the limits of error of judgment and technique inherent in human frailty.

TABLE 1. FIFTY PATIENTS WITH REGROWTH OF GOITER

Prior operation performed elsewhere, in 25.
Prior operation performed by us, in 25.
Hyperthyroidism in 34, 15 of whom had *persistent* hyperthyroidism, and 19 *recurrent* hyperthyroidism after an interval of health or of hyperthyroidism.
Normal metabolic status in 16, 9 having been thyrotoxic before prior operation.
No patient in whom hyperthyroidism accompanied the regrowth was thought to have previously had a nontoxic goiter, but the converse was frequently found.

5. The maintenance of a normal metabolic status in postoperative hypothyroidism should offer no more difficulty than in the case of spontaneous hypothyroidism.

Nearly twenty years ago, we were abandoning the old concept that one could regularly accomplish two mutually exclusive objectives in the operating room, namely, 1) to remove sufficient toxic goiter to give absolute relief of hyperthyroidism, and 2) to leave enough toxic goiter to meet the patient's need for thyroxine. We did not then and do not now believe that such a result can be produced with regularity and the writer knows of no published report to substantiate a view contrary to our own. Postoperative results are nearly meaningless in regard to the risk of recurrence after an interval of health or even of hypothyroidism, if they are confined to patients followed for less than fifteen years. Persistent hyperthyroidism, of course, means that the patient does not regain an unequivocally normal status without the postoperative administration of iodine or other suppressive therapy as a measure of further control.

The present report is made to evaluate, by a study of all the private case records in the writer's possession, the results of the plan as formulated in 1932 and the validity of the concepts on which it is based. Radical subtotal thyroidectomy for bilateral toxic goiter has been the type of operation used since that time and the amount of goitrous tissue left on each side has not been thought to exceed one gram in weight.

COMMENT

1. The tabulated data (Tables 1–5) present the facts pertinent to this report which is concerned only with those 34 patients in whom hyperthyroidism persisted or recurred after operation performed by us (the late Willard Bartlett and the writer) or by surgeons elsewhere. It will be seen at once that the two-stage thyroidectomy, as used by us as late as 1937 in poor-risk patients, was followed by failure to cure the disease in 9 of the 19 cases we originally operated upon (Cases 17A, 24, 26, 43 in Table 2;

TABLE 2. PERSISTENT HYPERTHYROIDISM

Prior op. here (9 patients)				Secondary op.	Result
17A	E.B.	d.h.*	*2-stage*, '29	L. lobe, '36	H.**'51
20A	M.H.	d.h.*	1-stage, '30	Bilat., '51	H.
21	M.S.	d.h.*	1-stage, '30	Bilat., '37	H. '51
24	E.B.	d.h.*	*2-stage*, '30	Refused, '35	?
26	M.M.	d.h.*	*2-stage*, '30	Bilat., '41	H. '45
43	R.K.	d.h.*	*2-stage*, '34	Bilat., '37	H. '42
269	E.K.	d.n.†	1-stage, '38	Intrathoracic, '40	H. '43
655	F.B.	u.ad.‡	L. lobe, '46	Refused, '46	?
722	L.B.	d.n.	1-stage, '47	Pyramidal, '49	H. '51
Prior op. elsewhere (6 patients)					
113	M.G.	d.h.	1-stage, '33	*2-stage*, '37	Rec. '47§
376	V.F.	d.h.	1-stage, '29	R. lobe '39	Death
615	M.A.	d.h.	1-stage, '40	Bilat., '42	H. '45
1084	R.F.	d.h.	1-stage, '45	Preop. Rx, '51	
765	C.W.	d.n.	L. lobe, '45	R. lobe, '47	H. 4 mo.
1062	S.R.	d.n.	L. lobe, '30	R. lobe, '51	Normal

* d.h. = diffuse hyperplasia.
** H. = hypothyroid, treated.
† d.n. = diffuse nodular.
‡ u.ad. = unilateral adenoma.
§ Bilateral recurrence; thyrotoxic; operated on again in 1948.

and 25, 51, 93, 113, 160 in Table 4). The explanation of this failure lies in a technical step which was involved when lobectomies were performed at two sittings; after turning flaps of skin and fat, the platysma and deep cervical fascia were incised longitudinally, *not* in the midline, but to the right or to the left side. This procedure served the purpose of avoiding encroachment on the contralateral operative field at any one stage, but sometimes resulted in failure adequately to visualize the isthmus and trachea completely on one or both occasions. Too much tissue was unwittingly left immediately adjacent to the trachea in these patients, all of whom

TABLE 3. RECURRENT HYPERTHYROIDISM: INTERVAL EVENTS

No. of cases	Period of recognition of toxicity
2	2 years or less
3	2 to 5 years
3	5 to 10 years
11	10 years or longer
19 Total	

16 patients did *not* become hypothyroid
3 patients became hypothyroid

TABLE 4. RECURRENT HYPERTHYROIDISM

			Prior op. here (10 patients)	Secondary op.	Result
4	F.S.	d.h.*	1-stage, '25	Bilat., '38	H.** '51
23	W.I.	d.h.*	1-stage, '30	Bilat., '34	H. '51
25	E.L.	d.h.*	*2-stage*, '30	Bilat., '35	H. '51
30	M.M.	d.h.*	1-stage, '31	Bilat., '39	H. '47
51	A.H.	d.h.*	*2-stage*, '35	Bilat., '44	H. '50
35	C.O.	u.ad.†	R. lobe, '33	L. lobe, '50	H. '51
91‡	L.D.	d.h.	1-stage, '36	Bilat., '50	H. '51
93	M.D.	d.h.	*2-stage*, '36	L. lobe, '48	H. '49
113‡	M.G.	d.h.	*2-stage*, '37	Bilat., '48	H. '49
160‡	G.W.	d.h.	*2-stage*, '37	Bilat., '47	H. '51
			Prior op. elsewhere (9 patients)		
94	B.M.	u.ad.	R. lobe, '23	L. lobe, '36	Normal, '38
159	A.J.	d.h.	1-stage, '27	Bilat., '37	H. '51
242	R.O.	d.h.	1-stage, '23	Refused op., '38	?
284	A.G.	d.h.	1-stage, '21	Refused op., '38	Sl. toxic, '51
348	R.J.	d.h.	1-stage, '27	Refused op., '39	?
577	E.P.	d.h.	1-stage, '25	Not rec., '41	Controlled, '46‖
623	C.C.	d.h.	1-stage, '41	Bilat., '44	H. '50
757	R.W.	d.n.§	L. lobe, '20	Bilat., '47	H. '48
812	L.N.	d.h.	1-stage, '36	Bilat., '48	H. '51

* d.h. = diffuse hyperplasia.
** H. = hypothyroid, treated.
† u.ad. = unilateral adenoma.
‡ Taking thyroid substance from time of operation to recurrence.
‖ Died at 78 after stroke.
§ d.n. = diffuse nodular.

were operated upon for diffuse hyperplastic goiter with or without exophthalmos.

2. Of the 6 patients (Cases 20A and 21 in Table 2; and 4, 23, 30, 91 in Table 4) with diffuse hyperplastic goiter who were not cured after a one-stage operation performed by us, all except 1 (Case 91) underwent the conservative bilateral resection employed in 1932 and earlier. This patient operated upon in 1936, is the only one with Graves' disease known to the

TABLE 5. SUMMARY OF PERSISTENT AND RECURRENT CASES OF HYPERTHYROIDISM

Total number of cases			34
Prior operation elsewhere	15		
Prior operation by us	19		
Primary operations performed by us (19 cases)			
Diffuse hyperplasia of the thyroid		15	
2-stage resection in 1929–1937	9		
1-stage bilat. resection in 1925–1936	6		
5, conservative op., 1925–1931			
1, in 1936			
Toxic nodular goiter		4	
"unilateral" adenoma; lobectomy only (1946, 1933)	2		
1 persistent			
1 recurrent in other lobe 17 yrs. later (Ca)			
multinodular	2		
1 intrathoracic; separate component overlooked (1938)			
1 failure to excise pyramidal lobe (1947)			
Results of secondary operations (28 cases)			
1 death on first postoperative day, due to cardiac arrest, not crisis.			
1 recurrence of hyperthyroidism after 10 years; operation repeated.			
2 patients in normal metabolic status when last seen.			
24 patients promptly became hypothyroid and have remained so; they are maintained in normal metabolic status by oral administration of thyroid substance.			

writer in whom there has been failure to obtain complete and, to date, permanent cure by radical one-stage subtotal thyroidectomy.

3. Of the 4 failures to achieve cure after primary operation for nodular toxic goiters performed by us, 2 occurred in patients who were considered at operation to have discrete, unilateral adenomata in an otherwise normal gland. One of these patients (Case 35, Table 4) had an interval of perfect health for seventeen years after unilateral lobectomy but returned at the age of 76 with intense hyperthyroidism of six months' duration due to a similar adenoma of the remaining lobe; this adenoma was found to include an area of cystadenocarcinoma and the lobe was totally removed. In another patient (Case 655, Table 2), a very large adenomatous left lobe,

seriously deflecting the trachea, was removed and one small adenoma was excised from the opposite lobe, which appeared to be otherwise grossly normal. That this gross evaluation was erroneous is proven by the persistence of hyperthyroidism, undoubtedly due to diffuse hyperplasia in the remaining lobe. The patient improved moderately with thiouracil administration, refused a second lobectomy repeatedly, and cannot be traced.

The remaining 2 patients with adenomatous goiter had bilateral, grossly multinodular glands. In 1 (Case 269, Table 2) the coexistence of an intrathoracic component some 3 inches in diameter, which had lost all continuity with the lower poles of the lateral lobes, was overlooked at primary subtotal thyroidectomy. Obvious, persistent hyperthyroidism prompted x-ray examination of the thorax and recognition of the lesion. Cure followed excision and administration of thyroid substance was necessary thereafter until the patient's death five years later from metastasizing carcinoma of the ovary. In the second such patient (Case 722, Table 2) the writer failed to identify the pyramidal lobe at primary, bilateral operation, but the subsequent persistent, mild hyperthyroidism disappeared following excision of the pyramidal lobe two years later. The patient is now taking a maintenance dose of thyroid substance daily.

4. Little comment is profitable as to the earlier history of the 15 patients whose first operation had been done elsewhere. A clear notion of the reason for the failure to achieve cure was often obtainable from review of a previous hospital record, from the finding of intact enlarged upper poles in which the superior thyroid vessels had not been divided, and from the occasional enlargement of the remaining lobe after hemithyroidectomy. It is not unfair to state that the previous surgeon had not had a concentrated experience in surgery of the thyroid. Technical errors such as are described in our own failures, were usually apparent, *i.e.*, either improper pathologic evaluation or concentration on how much tissue was being removed rather than on how little was being left.

5. The results of the 28 secondary operations which we performed supply further evidence that a sufficiently radical operation will result in cure of hyperthyroidism. In Case 113 (Table 2) the patient had persistent hyperthyroidism, having been operated upon elsewhere in 1933 for exophthalmic goiter. A two-stage thyroidectomy in 1937 after four months of preparatory treatment was followed by good health. She took maintenance doses of thyroid until 1945, when she was found to have a basal metabolic rate of minus 19 per cent and palpable thyroid tissue bilaterally adjacent to the trachea. She failed then to take the recommended dosage of thyroid and returned in 1947 with moderate hyperthyroidism (Table 4) which was completely relieved by tertiary bilateral operation in 1948.

One postoperative death occurred in this group (Case 376, Table 2)

due to sudden cardiac arrest in an elderly patient who had had a smooth postoperative course for twenty hours following the first lobectomy of a planned two-stage operation in 1939. She had had three months of modified bed rest, including a period of hospitalization because of vomiting, and met our minimum criteria of operability. The writer has had only 1 death following thyroidectomy since this event; in 1947, a hypertensive patient with a huge goiter went into irreversible shock upon the occurrence of massive, left-sided pulmonary atalectasis when the intratracheal tube employed during anesthesia was not removed promptly afterward, and slipped distally far enough to obstruct the left main-stem bronchus.

The high percentage of follow-up and its duration since secondary operation are significant. Only 2 of the patients have failed to require maintenance doses of thyroid substance.

SUMMARY

A study of the 34 patients with postoperative recurrent or persistent hyperthyroidism, of whom the writer has record, justifies the following statements:

1. Persistent or recurrent hyperthyroidism is due only to leaving too much goitrous tissue at primary operation.

2. The performance of a "conservative" thyroidectomy, improperly labeled "subtotal," in an effort both to cure the disease permanently and yet to avoid postoperative myxedema, will risk an unduly high rate of unsatisfactory results and should be abandoned.

3. The radical subtotal thyroidectomy as we have performed it since 1932 will produce permanent cure of hyperthyroidism with the utmost regularity. With rare exceptions, postoperative euthyroid status must be maintained by thyroid feeding, the need for which will be life-long. This program must be thoroughly explained to the patient.

4. The performance of total thyroidectomy is not necessary in order to achieve these results. Published data continue to support the view that a higher percentage of injuries to the recurrent laryngeal nerve and to the parathyroid bodies is seen after total thyroidectomy than after subtotal thyroidectomy.

A STUDY OF THE ANKLE JERK IN MYXEDEMA*

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SLOWNESS of movement is one of the prominent symptoms of patients who have myxedema. It is observed not only in voluntary movements, but also in the response of the tendon reflexes. As a simple test of this aspect of the disease, observation of the speed of muscular movement elicited by the tendon reflexes, particularly those of the biceps and Achilles tendons, has proven to be useful in diagnosis. Usually a definite slowing of the reflex response can be observed in patients with myxedema during the routine clinical examination.

At the Mayo Clinic, use of this test as an aid in the diagnosis of myxedema began at least thirty years ago when it was recognized that myxedema was probably the only condition in which a characteristic "delayed relaxation" of the tendon reflexes was observed. Graphic records to demonstrate this were not made until 1924, when Chaney (1) reported measurements of the duration of the ankle jerk in patients with myxedema and other conditions. He found that the reflex response was prolonged in patients with myxedema, but not in patients with low basal metabolic rates associated with certain other conditions. During treatment of myxedema, the response returned to normal. Similar observations were reported by Harrell and Daniel (2) in 1941.

In addition to these studies, there are numerous reports of isolated cases of myxedema in which slowing of the reflex response was observed (3–8). In some of these reports, the author considered slowing of the reflex response to be a relatively uncommon occurrence in myxedema. None of the published reports however, has included observations on a sufficient number of patients to reveal the frequency of this phenomenon in myxedema or to permit a critical evaluation of its usefulness as a diagnostic sign. It was the purpose of the present study to determine the frequency with which slow-

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ing of the reflex response occurs in patients with myxedema and to investigate some of the possible mechanisms of its occurrence. The reflex chosen for study was the ankle jerk or Achilles tendon reflex.

METHODS

Measurements of the ankle jerk were made with the subject seated. The subject's left foot was placed on a hinged platform (Fig. 1) and his position was adjusted so that the lower segment of the leg was vertical and so that the knee joint formed a right angle. His foot was slightly dorsiflexed by the inclination of the platform. A 5-kilogram weight was placed on the knee to hold the heel in contact with the platform.

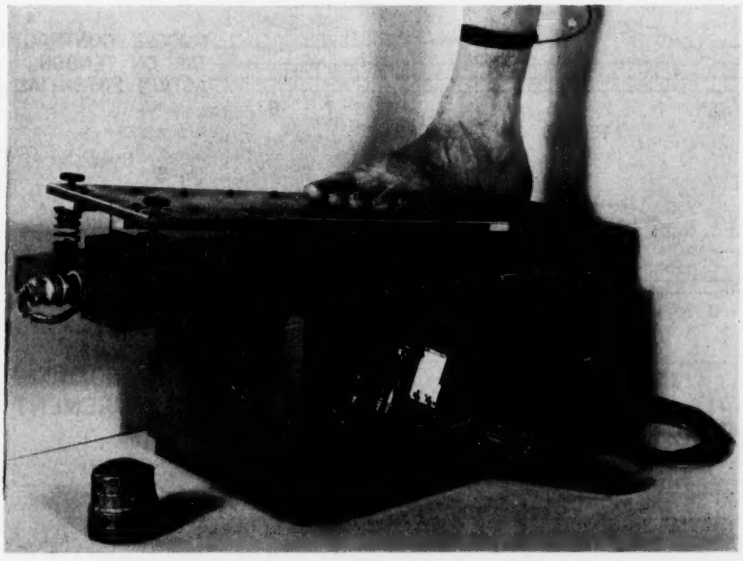

FIG. 1. Apparatus for measuring the ankle jerk. Pressure of the foot on the platform is measured by a resistance wire pressure transducer. Springs on either side of the transducer permit adjustment of the initial pressure. The platform is calibrated by placing the 1-kilogram weight at the position occupied by the ball of the foot. Movement of the platform during the reflex response is less than 0.001 inch.

The force of the tap on the tendon was measured by a resistance wire accelerometer (9, 10) attached to the percussion hammer. Pressure of the ball of the foot on the platform during reflex contraction of the calf muscle was measured by a resistance wire pressure transducer (9, 10). The electrical action potential of the calf muscle was detected by surface electrodes on the belly of the muscle and near the tendon of the muscle or by needle electrode. Records were made photographically by a galvanometer oscil-

lograph (Fig. 2) and, in some studies, records of the electrical activity of the muscle were made also by cathode ray oscilloscope.

During the entire procedure, the temperature, deep in the calf muscle, was measured by a thermocouple or thermistor cemented into the tip of a hypodermic needle (25 gauge, 3.8 cm. in length) which was inserted to a depth of 3.5 cm. below the skin surface.

Many records of the ankle jerk could be obtained easily in a few minutes. Facilitation of the reflex response by a maneuver such as clenching

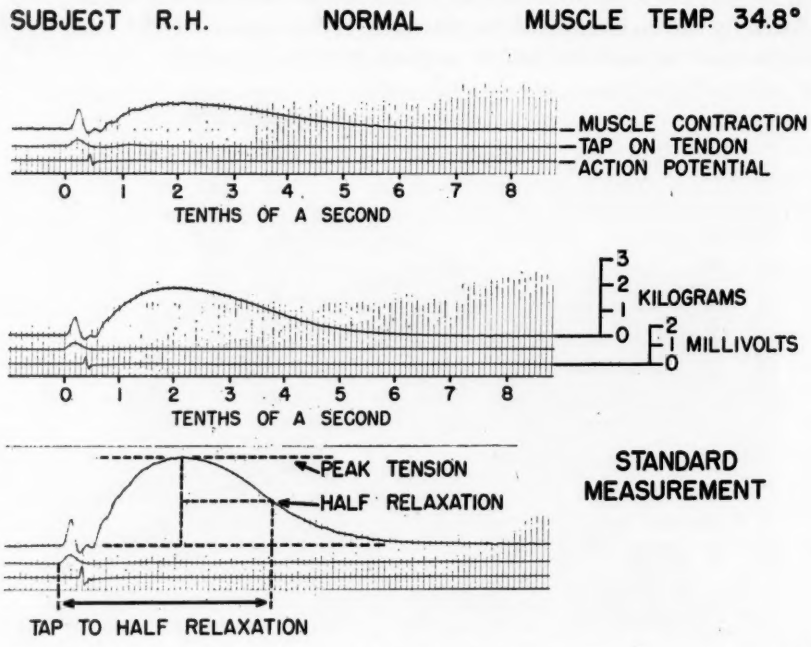

FIG. 2. Records of the ankle jerk of a normal subject. The three responses are from a series elicited at one sitting. The vertical lines are at 0.01 second intervals. Temperature is in degrees Centigrade. The initial deflection in the record of muscle contraction is produced by jarring of the foot by the tap on the tendon.

the fist was necessary in only a few instances, but it did not alter the character of the response. In only 6 of the 286 persons was it impossible to obtain a reflex response suitable for measurement.

Since it was difficult to elicit responses of the desired intensity at will, responses of various intensities were recorded in a random order. Generally, only weak reflex contractions were elicited (0.5 to 3.0 Kg. pressure on the ball of the foot), since stronger responses often were complicated by spread of the reflex to other muscle groups.

For accurate measurement of the duration of the reflex response, neither the time of the peak of contraction nor the end of relaxation was a sharp end point. Consequently, the time elapsed between the tap on the tendon and the moment when the muscle had relaxed half way has also been measured and has been used in this report as the standard measure of duration of the ankle jerk (Fig. 2). Since this time varies with the strength of contraction, several responses were measured and the force of contraction of each was plotted against its duration (Fig. 3). By interpolation, the

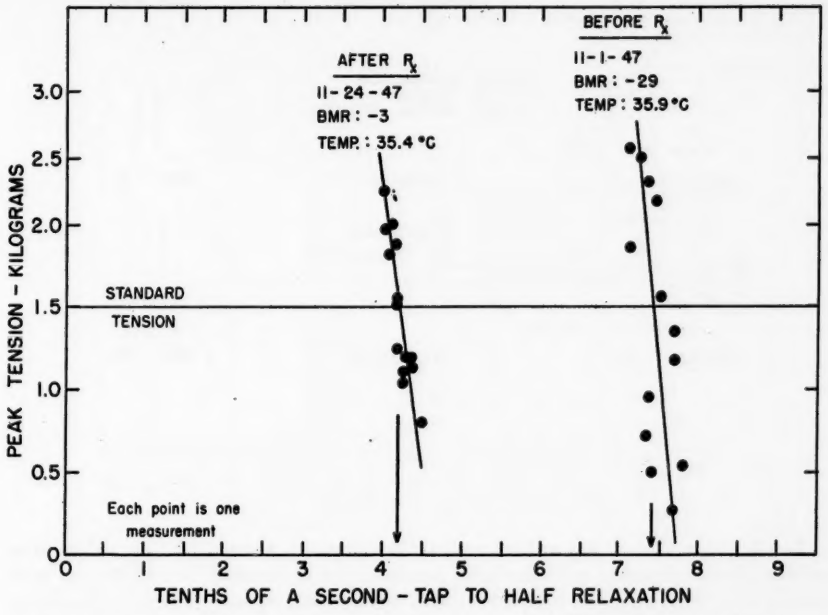

FIG. 2. Method of estimating the mean duration of the ankle jerk. By interpolation, the mean duration of a response with a peak tension of 1.5 Kg. is determined. The arrows point to the mean value for each set of measurements. Each set of measurements was taken at one sitting of a patient with myxedema before and after treatment.

mean duration of a response having a peak tension of 1.5 Kg. was obtained. This value has been used as the measure of duration of the ankle jerk in the studies being reported, unless other measurements are referred to specifically.

No attempt was made to achieve rigid basal or standard conditions for these studies. Generally, the tests were performed after the person had been seated for ten to thirty minutes after having walked to the laboratory. Records were made at different times during the day, however.

Reliability of the method.—To determine the reliability of the method of measuring the ankle jerk, 48 duplicate determinations of the mean duration of the ankle jerk were made on 40 persons (22 healthy adults and 18 myxedematous patients). The second determinations were made from one to eight hundred days after the first. The mean difference between the first and second tests was 0.026 second. Individual differences were less than 0.03 second in 66 per cent of cases and less than 0.06 second in 95 per cent of cases. No difference was greater than 0.07 second.

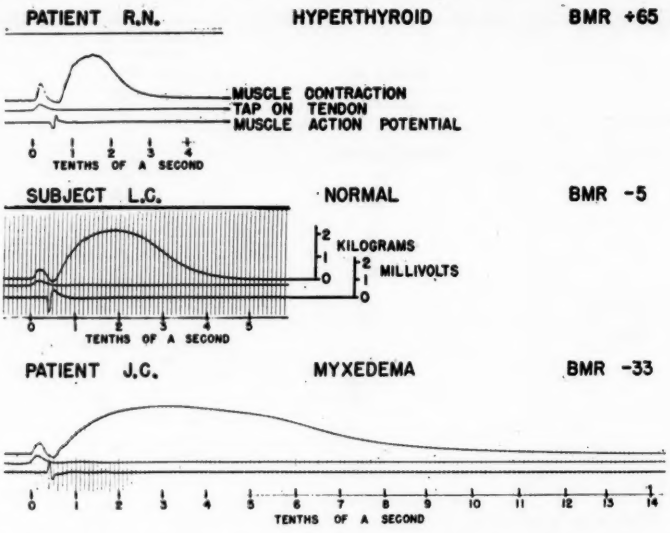

FIG. 4. Examples of the ankle jerk in hyperthyroid, normal and myxedematous persons. The contraction and relaxation phases of the response of the muscle are both prolonged in myxedema. In comparison with the normal response, however, the relaxation time is increased relatively more than the contraction time. In addition, the first half of the relaxation phase is often prolonged more than the last half. The appearance of an "angle" or shoulder in the relaxation phase is not uncommon.

The position of the subject's leg and foot and the temperature of the calf muscle were probably the principal variables causing day-to-day differences in response. Measurements of deep muscle temperature were made in 29 of the duplicate tests just described. In 21 instances the difference in temperature on different days was less than 1.0° C. In the 8 remaining instances, differences ranged from 1.0° to 3.0°. Corrections for differences in temperature reduce the differences between duplicate measurements of the ankle jerk. In a preliminary analysis, however, such corrections did not have a significant effect on the relative distribution of values for the duration of the ankle jerk in various groups of patients studied. Conse-

TABLE 1. MEAN DURATION OF PHASES OF THE ANKLE JERK IN VARIOUS CONDITIONS

Condition	Basal metabolic rate		Muscle temperature		From start of tap to ½ relaxation*		From start of tap to start of potential		Duration of potential		From start of potential to peak of contraction†		From peak of contraction to end of relaxation	
	N‡	Per cent	N‡	Degrees centigrade	N‡	Second	N‡	Milliseconds	N‡	Milliseconds	N‡	Second	N‡	Second
I. No thyroid disease														
a. Normal subjects	30	− 8.1±1.1§	20	35.9±0.28	35	0.34±0.0097	29	35±0.7	29	16±0.5	35	0.15±0.004	35	0.37±0.016
b. Miscellaneous patients	38	− 1.7±1.0	11	35.0±0.50	39	0.36±0.0081	17	35±0.8	17	¶7±0.7	39	0.16±0.003	39	0.43±0.017
c. Myotonia	1	+13.0	8	35.5±0.25	9	0.29±0.0097	7	35±0.8	7	17±1.0	9	0.13±0.004	9	0.33±0.020
d. Obesity	8‖	− 2.6±2.3			8	0.39±0.017					8	0.16±0.009	8	0.48±0.040
e. Low basal metabolic rate without myxedema	16¶	−19.3±0.9	10	35.1±0.37	16	0.39±0.012	14	35±0.7	14	17±0.6	16	0.17±0.004	16	0.48±0.019
II. Hyperthyroidism	26	+38.6±3.1	20	35.7±0.24	26	0.26±0.0081	24	38±0.7	24	18±0.1	26	0.12±0.004	26	0.26±0.013
III. Myxedema														
a. Spontaneous	68	−25.8±0.8	55	34.8±0.16	68	0.54±0.012	64	34±0.4	64	17±0.4	68	0.22±0.004	68	0.74±0.028
b. Postoperative or postradiation	39	−20.2±1.0	29	35.0±0.23	39	0.51±0.0072	36	36±0.5	36	17±0.2	39	0.21±0.005	39	0.69±0.029
c. With Addison's disease	1	−18	1	35.3	1	0.58	1	35	1	20	1	0.22	1	0.87
d. With hypopituitarism	5	−26.4±2.6	4	34.1±0.72	5	0.52±0.025	5	40±2.6	5	20±1.9	5	0.21±0.013	5	0.60±0.028
e. Thiocyanate myxedema	2	−18, −10	2	31.4, 34.9	2	0.60, 0.43	2	36, 30	2	19, 17	2	0.25, 0.20	2	0.95, 0.50

* Standard measure of duration referred to in the text.
† When the action potential had not been recorded measurements were begun 0.035 second after the start of the tap.
‡ N is the number of persons.
§ Mean and its standard error.
‖ These patients are also included in the group of miscellaneous conditions.
¶ This group includes 4 persons from the normal group and 2 patients from the miscellaneous group (see text).

quently, temperature corrections of the data have not been made in this report.

OBSERVATIONS

Measurements of the ankle jerk of 280 persons have been made. The data of 44 of these persons have been excluded from consideration in this report however, either because an unquestionable diagnosis of the patient's condition could not be established or because the patient was under treatment at the time of the test. The remaining 236 persons have been divided into three major categories according to whether they had myxedema, hyperthyroidism or no thyroid disease. The general character of the reflex response in each of the three categories is shown in Figure 4, and measurements of the basal metabolic rates, muscle temperature and various phases of the ankle jerk are summarized in Table 1. Some details concerning the various groups of persons studied and the duration of the ankle jerk in each are given in the following paragraphs.

I. *No thyroid disease*

Normal subjects.—The 35 persons who constituted the normal group were laboratory personnel and other healthy adults (15 men and 20 women) who were not patients at the clinic. Their basal metabolic rates ranged from +1 to −20 per cent. The mean duration of the ankle jerk (tap to half relaxation) of this group was 0.34 second, whereas the standard deviation of all values was 0.057 second. The actual range of values in this group was 0.21 to 0.45 second, which approximates closely the probable range (0.22 to 0.45) estimated to include 95 per cent of normal values as determined by the mean value plus or minus twice the standard deviation. There was no significant difference between the responses of men and women (mean difference 0.006 second, $p > 0.05$).

Miscellaneous conditions without thyroid dysfunction.—Thirty-nine patients (11 men and 28 women) were taken at random from persons referred for basal metabolic rate determinations, but who were found to have no clinical evidence of thyroid dysfunction. It included 9 patients whose examinations revealed no abnormalities, 6 with functional disorders, 8 with obesity, 6 with essential hypertension, 2 with muscle cramps and 8 with various other disorders. The mean duration of the ankle jerk of this entire group (0.36 second) was essentially the same as that of the normal subjects. The range of values in this group was 0.28 to 0.46 second (standard deviation, 0.047 second).

The mean duration of the ankle jerk of the 8 obese patients in this group (0.39 second) was slightly, but significantly, greater than that of normal subjects (mean difference 0.05 second, $p = 0.02$). There was, however, no

significant difference from the normal group in the mean duration of the ankle jerk of patients with no detectable abnormalities (mean, 0.36 second), of patients with functional disorders (mean, 0.36 second) or of those with essential hypertension (mean, 0.35 second).

Low basal metabolic rate without myxedema.—This group is composed of 16 patients (4 men and 12 women) whose basal metabolic rates were less than −13 per cent (range, −14 to −27 per cent) with no evidence of organic disease. In this group are included the data on 4 persons who are also in the normal group and 2 who are also in the miscellaneous group already described. The remaining 10 are patients who are not included in any other category. The mean duration of the ankle jerk in these patients (0.39 second) was slightly, but significantly, longer than that of the normal group (mean difference, 0.05 second, $p = 0.001$), but all values (range, 0.28 to 0.45 second) were within the range determined for normal subjects.

Myotonia.—The 9 patients with myotonia included 7 with myotonia congenita and 2 with myotonia dystrophica. The mean duration of the ankle jerk in this group was 0.29 second (range, 0.24 to 0.33 second). This was significantly less than normal (mean difference, 0.05 second, $p = 0.003$), although all values were within the normal range.

II. *Hyperthyroidism*

Twenty-six patients with hyperthyroidism (17 men and 9 women) had a mean duration of the ankle jerk of 0.26 second (range, 0.18 to 0.35 second). This was significantly less than the normal mean (difference, −0.09 second, $p < 0.001$). More than 75 per cent of the values however, were within the normal range.

III. *Myxedema*

The 115 patients (29 men and 86 women) in this category included 68 patients with spontaneous myxedema, 31 with postoperative myxedema, 8 with post-radiation myxedema, 5 with myxedema associated with hypopituitarism, 2 with thiocyanate myxedema and 1 with myxedema associated with Addison's disease. There was essentially no difference in the duration or character of the ankle jerk between the various groups (Table 1). For the entire group of myxedematous patients, the mean duration of the ankle jerk was 0.53 second. The standard deviation of all values was 0.083 second. Their distribution however, was slightly skewed toward the longer duration (Fig. 5). The actual range of values was from 0.34 to 0.80 second.

The mean duration of the ankle jerk in myxedema was distinctly longer than normal. When considering the usefulness of observations of the ankle jerk for the diagnosis of myxedema, however, it is necessary to determine the extent to which values of the myxedematous patients overlap those

of the euthyroid group. If the upper limit of the euthyroid range is taken to be 0.46 second, approximately 23 per cent of myxedematous patients had a value for the duration of the ankle jerk which fell within the euthyroid range (Fig. 5). No patient without myxedema had a value greater than 0.46 second, however.

The standard measurement (tap to half relaxation) was superior to other measurements of the ankle jerk in this respect. The contraction time and the total relaxation time of the reflex response were both prolonged in myxedema, but 45 per cent of values for the contraction time and 35

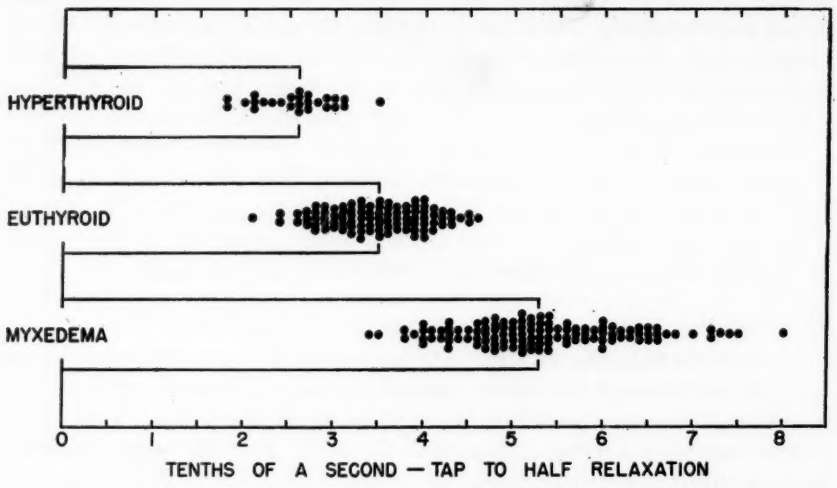

FIG. 5. Distribution of measurements of duration of the ankle jerk in hyperthyroid, euthyroid and myxedematous persons. Each point represents 1 person. All patients in each category of Table 1 are represented. The bars indicate the mean duration of the ankle jerk for each group.

per cent of values for the relaxation time fell within the euthyroid range. Similarly, 34 per cent of values for the total duration of contraction plus relaxation fell within the euthyroid range.

Relation of duration of ankle jerk to thyroid activity.—It is evident from the distribution of values for the duration of the ankle jerk in hyperthyroid, hypothyroid and euthyroid persons shown in Figure 5 that there is a relationship, either direct or indirect, between activity of the thyroid gland and the duration of the reflex response. To explore this further the basal metabolic rate has been used as an indirect index of thyroid function to which the duration of reflex response might be related. Values for three groups of persons have been plotted in Figure 6. Data on all patients in the hyperthyroid and hypothyroid groups are included, but only the groups

of normal subjects and miscellaneous patients have been included in the euthyroid category. Furthermore, patients with essential hypertension were excluded from the miscellaneous group, because they often had elevated basal metabolic rates, presumably of nonthyroidal origin.

Points plotted in this way (Fig. 6) suggest a curvilinear relation between thyroid function and the duration of the ankle jerk. This would be an interesting relationship, if true. However, the points plotted in Figure 6 represent three different groups of people and an assumption that a continuous curve can be constructed from them may not be valid.

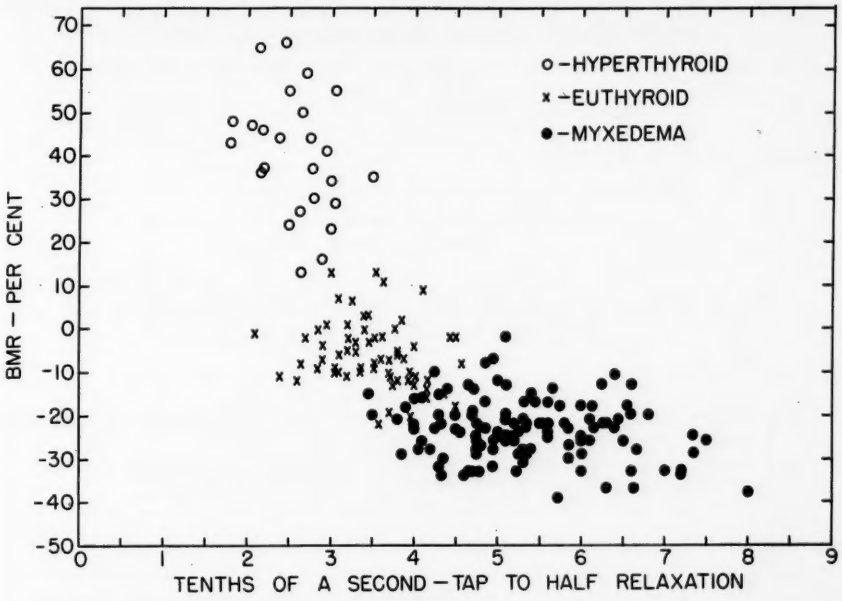

FIG. 6. Relation of the duration of the ankle jerk to the basal metabolic rate in hyperthyroid, euthyroid and myxedematous patients. Each point represents measurements on 1 person. See text for conditions included in the euthyroid group.

There is, however, a slight, but significant, correlation between basal metabolic rate and duration of the ankle jerk in normal subjects (correlation coefficient 0.40, $p < 0.05$). This relationship should be explored further, using a more direct measure of thyroid activity and an adequate measure of rate rather than duration of muscular contraction and relaxation.

Effect of treatment of myxedema.—The effect of treatment with desiccated thyroid on the duration of the ankle jerk was studied in 55 myxedematous patients. During treatment a decrease in duration of the ankle jerk, which generally paralleled the increase in basal metabolic rate (Fig. 7).

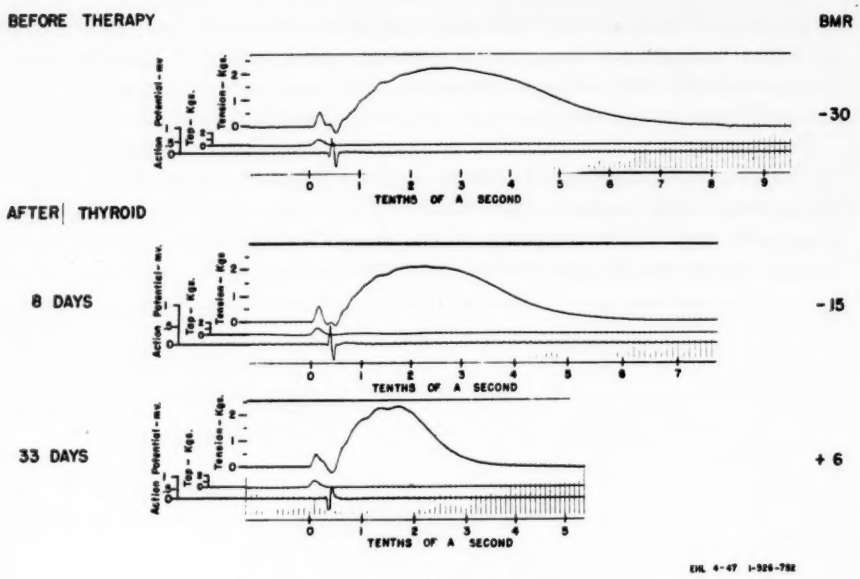

FIG. 7. Effect of treatment with desiccated thyroid on the duration of the ankle jerk in a patient with myxedema.

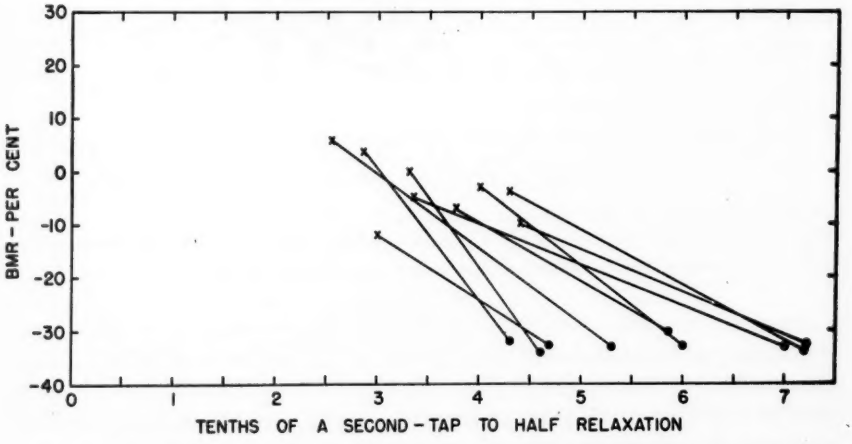

FIG. 8. The effect of treatment with desiccated thyroid on the basal metabolic rate and the duration of the ankle jerk in myxedema. Only patients whose initial basal metabolic rates were less than −30 per cent are included in this graph. The solid circles represent measurements prior to treatment. The crosses represent measurements after treatment. The lines connect measurements made on the same patient.

occurred in all patients. It occurred whether the ankle jerk response prior to treatment was within the normal range or not (Fig. 8). This indicates that slowing of the ankle jerk is probably a feature of the disease in all patients in whom myxedema develops, even though in some the slowing does not increase the duration of the ankle jerk beyond the normal range.

Two patients were followed during the development of myxedema after administration of radioactive iodine for malignant thyroid tumors. In these patients an increase in duration of the ankle jerk paralleled the decrease in basal metabolic rate (Fig. 9).

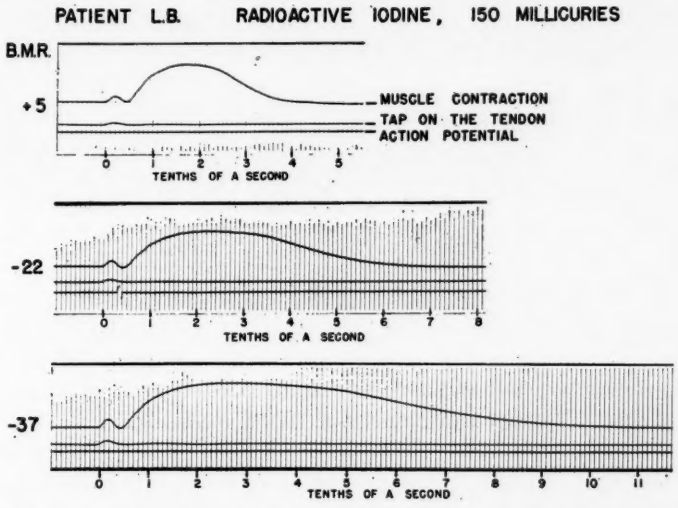

FIG. 9. Records of the ankle jerk during development of myxedema after administration of radioactive iodine. The first record was made immediately before administration of the drug. The second and third records were made six and ten weeks, respectively, after administration of the drug.

Studies on the mechanism of the slow response of tendon reflexes in myxedema.—Several mechanisms have been suggested to explain the slowness of the reflex response in myxedema. These include (a) abnormal activity of the central nervous system (5, 6), (b) a disorder of the muscle like that of myotonia,[1] (c) a lowered temperature of the muscle (11), (d) an increased viscosity of the muscle due to myxedematous infiltration (2), and (e) part of a general slowing of all vital processes (1). Thus far, we have examined the first three possibilities.

(a) Events in Reflex Excitation of the Muscle.—The possible role of

[1] A review of reports dealing with this possibility is given by Thomasen (7).

the speed of conduction over neural pathways of the reflex arc in producing the slow response of tendon reflexes in myxedema has been studied by measuring the latent period of the reflex and the action potential of the calf muscle. Such measurements were made on the majority of persons studied (Table 1).

The time interval between the beginning of the tap on the Achilles tendon and the beginning of the muscle action potential has been used as a measure of the latent period of the reflex. The means of these measurements in 29 normal subjects and 108 patients with myxedema were 0.035 second and 0.036 second, respectively (mean difference, 1 millisecond, $p > 0.05$). It can be concluded that there was no appreciable difference in the speed of conduction through the reflex arc in normal and myxedematous persons.

It should be borne in mind that the Achilles tendon reflex occurs over a two-neuron reflex arc which does not involve conduction through interneurons, so that the latent period is largely due to conduction over peripheral nerves. It cannot be concluded from the measurements just discussed that more complex activity of the central nervous system is not appreciably altered in myxedema.

The spread of excitation over the calf muscle was studied by observing the contour and duration of the muscle action potential. No consistent difference in contour of the synchronized action potential of the muscle was observed in normal and myxedematous persons and, again, there was no significant difference between these two groups in the mean duration of the action potential. The mean duration of the first two phases of the action potential was 16 milliseconds and 17 milliseconds in normal and myxedematous persons, respectively (mean difference, 1 millisecond, $p > 0.05$).

It is not impossible that more exact technics may disclose a small, but significant, difference in both latent period and action potential between these two groups. A small difference might be expected, because of the slight difference in body temperature between normal and myxedematous persons. However, the difference must be rather small and could not account for the large differences in response of the muscle.

The possibility existed that the prolonged response of myxedematous muscle is in the nature of a tetanus rather than a single response of the muscle. This would be the case if a prolonged discharge of impulses occurred over motor neurons following the initial synchronized volley represented by the initial large action potential of the muscle. To determine whether this was the case, records were made of the electrical activity of the calf muscle using both surface and needle electrodes and high electronic amplification (Fig. 10).

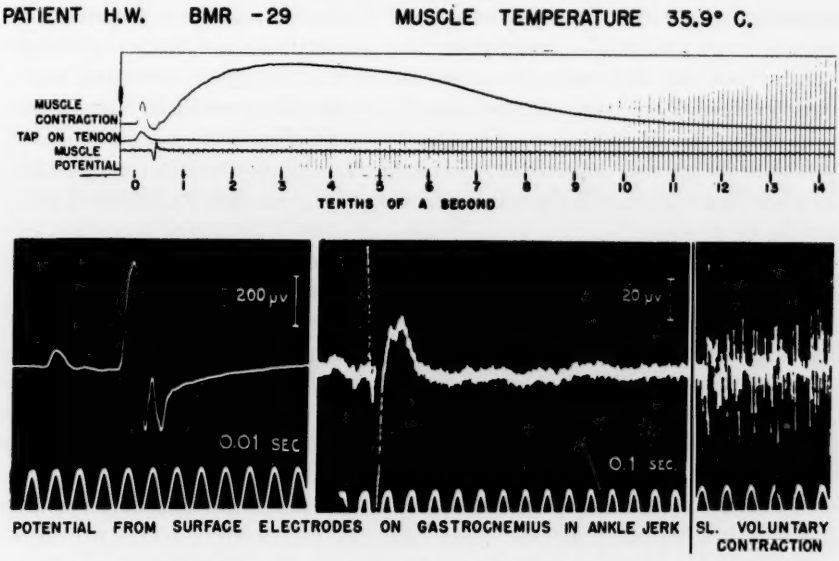
PATIENT H.W. BMR -29 MUSCLE TEMPERATURE 35.9° C.
MUSCLE CONTRACTION
TAP ON TENDON
MUSCLE POTENTIAL
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
TENTHS OF A SECOND
200 μv
0.01 SEC
20 μv
0.1 SEC.
POTENTIAL FROM SURFACE ELECTRODES ON GASTROCNEMIUS IN ANKLE JERK
SL. VOLUNTARY CONTRACTION

FIG. 10. Action potential of the calf muscle associated with the ankle jerk in a patient with myxedema. The upper tracing shows the duration of contraction of the muscle. The lower tracing shows details of the electrical action potential of the muscle recorded by cathode ray oscillograph with low amplification and fast writing speed in the first picture and with high amplification and slow writing speed in the second picture. The first small deflection in the first picture is a movement artefact due to the tap on the tendon. Note that there is no evidence of electrical activity following the initial synchronized action potential of the muscle. The fine irregularity of the base line in the second picture is an artefact associated with high amplification. Action potentials produced by a slight voluntary contraction are shown in the third picture.

No prolonged discharge of action potentials of motor units was observed which could explain the slow response of the muscle in myxedema. In most instances reflexes were not accompanied by an after-discharge. When motor unit action potentials did occur following the initial synchronized spike potential of the reflex response, they did not bear a constant relation to the mechanical events of the contraction from time to time or in different persons. Such a discharge seldom appreciably altered the contour or the duration of the mechanical response. We have considered these discharges to be only incidental to the reflex response. They most often occurred when a strong contraction was elicited.

It may be concluded from these studies that the slow reflex response in myxedema is not caused by an abnormality of the conduction and excitation mechanisms involved in the reflex contraction.

(b) Relation to Myotonia.—Another possibility is that prolonged

muscular contraction in myxedema may be due to repetitive responses of muscle fibers to a single stimulus such as occurs under a variety of circumstances in which delayed relaxation of muscle is observed, including veratrine poisoning, prostigmine poisoning, increased extracellular concentration of potassium, myotonia, and so on (12). However, no evidence of repetitive responses was observed during the reflex muscular contraction in myxedema when the electrical activity of the muscle was studied with needle electrodes.

Some authors have called the reflex response in myxedema a myotonic reflex because of the delayed relaxation of the muscle. They have assumed, perhaps, that the abnormality of the muscle is like that of myotonia congenita. Study of the electrical activity of the muscle in myxedema has not revealed activity like that which is characteristic of myotonia. Furthermore, the reflex response in myxedema is not like that of myotonia. The duration of the ankle jerk in myotonia was on the average shorter rather than longer than that of normal subjects (Table 1).

A single nerve volley such as that which reaches the muscle when the ankle jerk is elicited does not excite appreciable repetitive activity of muscle, and delayed relaxation of muscle in patients with myotonia whom we have studied takes place only after repetitive stimulation of the muscle such as occurs during voluntary contraction.

(c). Effect of Muscle Temperature.—Since the temperature of muscle is one of the principal variables affecting its speed of contraction, measurements of temperature deep in the calf muscle were made during measurement of the ankle jerk in the majority of patients (Table 1). In 91 myxedematous patients, the mean temperature was 34.8° C. (range, 31.4° to 37.0° C.). This was significantly lower (mean difference, 1.1° C., $p < 0.001$) than the mean temperature of the normal group, which was 35.9° C. (range, 34.6° to 37.2° C.). Although perusal of the mean temperatures of the individual groups of patients in Table 1 failed to suggest that this difference in temperature accounted for the slowness of the muscular response in myxedema, more definitive studies were carried out.

To determine the effect of muscle temperature on the duration of the ankle jerk, the muscle of normal and myxedematous subjects was allowed to cool by having the person remain sitting in a relaxed position for periods of time up to three hours, while the ankle jerk was tested periodically. In all of 44 persons tested, the muscle temperature fell continuously from the moment temperature measurements were begun. The fall of temperature during the first thirty minutes was 1.44 ± 0.12° C. and 1.41 ± 0.12° C., respectively, in 11 normal subjects and 13 myxedematous patients who were observed for thirty minutes or more. The difference between the two groups was not significant statistically ($p > 0.05$). After one hour the fall

of temperature was 2.5° C. and 2.4° C., respectively, in 11 normal subjects and 5 myxedematous patients.

An increase in duration of the ankle jerk paralleled the decrease in temperature. The mean increase in duration was 0.023 ± 0.0013 second and 0.028 ± 0.0037 second per degree Centigrade change in temperature, respectively, in 13 normal subjects and 14 patients with myxedema in whom a temperature change of 1° or more was observed. The difference between the groups was not significant ($p > 0.05$).

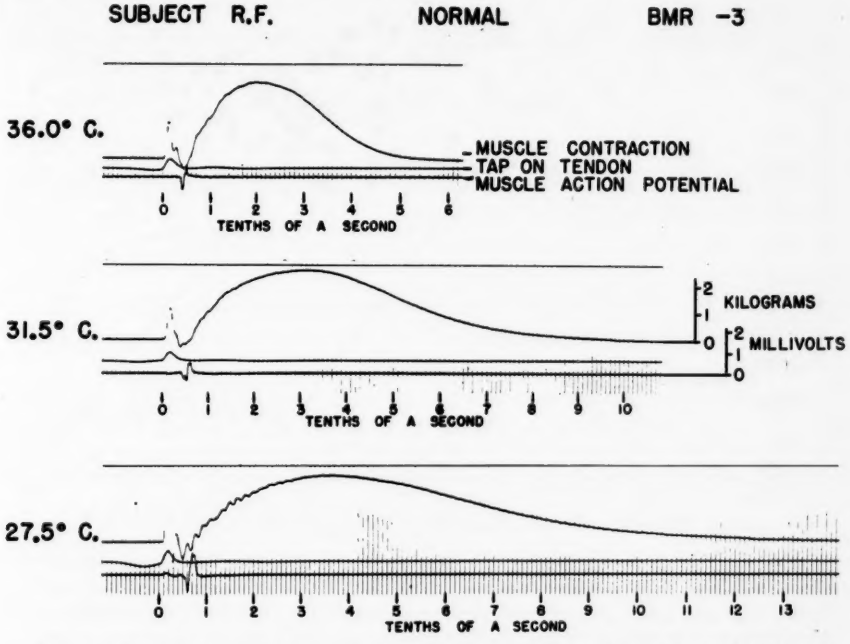

FIG. 11. Effect of muscle temperature on the duration of the ankle jerk. The calf muscle was cooled by means of ice packs to the temperature indicated on the left-hand side of the record.

The low magnitude of these values supports the conclusion that the slight difference in mean temperature between normal and myxedematous muscle does not account for the difference in duration of the ankle jerk.

In 5 normal subjects, it was necessary to lower the temperature of the calf muscle to between 25° and 28° C. by cooling with ice packs before the ankle jerk was prolonged to the extent seen in some patients with myxedema in whom muscle temperature was greater than 34° C. (Figs. 11 and 12). Furthermore, the response of cooled normal muscle differed in many respects from that of myxedematous muscle (Fig. 11). Cooling caused an

increase in duration of all phases of the reflex including the latent period and the action potential of the muscle, whereas in the reflex of myxedematous patients the latter events, on the average, were not appreciably different from those of warm normal muscle. There was also a difference in the

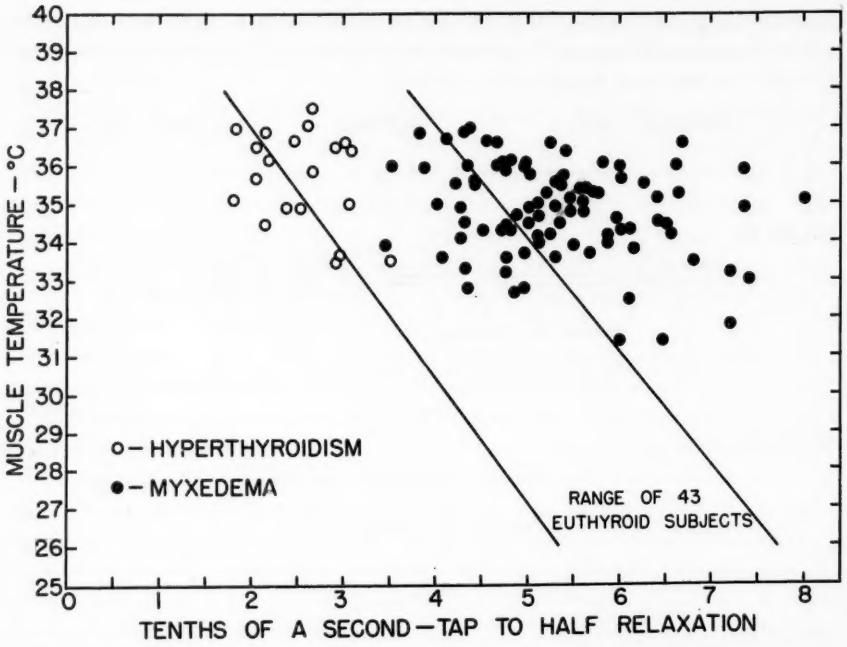

FIG. 12. The relation between temperature of the calf muscle and the duration of the ankle jerk. Each point represents 1 hyperthyroid or myxedematous patient. The range of values found in euthyroid persons is bounded by the two parallel lines. These lines have been extended to low temperatures on the basis of experiments in which the muscle was cooled by ice packs (see Fig. 11). Note that the reflex responses of 73 per cent of myxedematous patients fall outside of the normal range, even when temperature is taken into account.

relative prolongation of the different phases of the muscular response in normal subjects after cooling, and in myxedematous patients (Fig. 13). Relative to the increase in duration of other phases of the response, the first half of the relaxation phase was prolonged more in myxedema than it was in cooled normal muscle.

These observations further support the conclusion that a lower temperature of the muscle does not account for the slowness of the response of tendon reflexes in myxedema.

COMMENT

Measurements of graphic records confirm the clinical impression that an increase in duration of the ankle jerk is a useful sign for the diagnosis of myxedema. The duration of the ankle jerk was increased beyond the

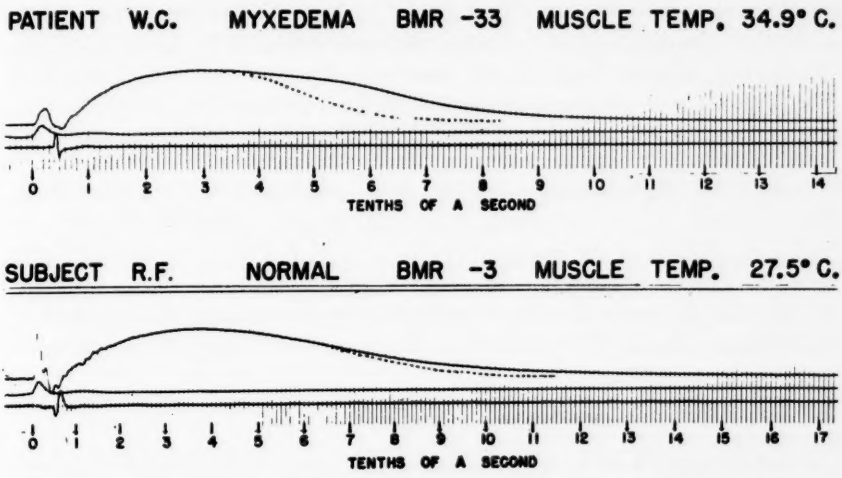
PATIENT W.C. MYXEDEMA BMR -33 MUSCLE TEMP. 34.9° C.
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
TENTHS OF A SECOND
SUBJECT R.F. NORMAL BMR -3 MUSCLE TEMP. 27.5° C.
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
TENTHS OF A SECOND

FIG. 13. Comparison of the ankle jerk of a patient with myxedema and of a normal subject whose muscle was cooled by ice packs. In the upper curve, the dotted line represents the relaxation phase of the response of the patient after treatment. The curve obtained after treatment has been plotted so that the contraction phase coincides with that of the curve before treatment. In the lower curve the dotted line represents the relaxation phase of the normal muscle when warm. The response of the warm muscle has been plotted so that the contraction phase coincides with that of the cooled muscle. Note that different phases of the response are affected more uniformly by cooling than by myxedema.

range of responses of euthyroid persons in 77 per cent of patients with myxedema. In this respect tests of the duration of the reflex response are probably more specific for the diagnosis of myxedema than the basal metabolic rate, since in persons with low basal metabolic rates without myxedema, the duration of the ankle jerk remained within the normal range. Other euthyroid categories must be examined to test the specificity of the prolonged reflex response further. However, Chaney (1) has already observed that 4 patients with pituitary tumors and 1 with anorexia nervosa who had low basal metabolic rates without myxedema had reflex responses which were within the normal range. Harrell and Daniel (2) observed that their measurements of the reflex responses of patients with low basal metabolic rates associated with nephrosis (3 cases) and anorexia

nervosa (1 case) were less than the range in their patients with myxedema (4 cases).

The duration of the ankle jerk is not a sensitive test of an increase in thyroid activity, since 75 per cent of hyperthyroid patients had measurements within the normal range. However, the fact that the mean duration of the response is shorter than normal in hyperthyroidism supports the view that the duration of the reflex response is related to thyroid activity. Previously, Mussio Fournier (8) also had observed that the duration of the response was shorter than normal in his 3 patients with exophthalmic goiter, but Harrell and Daniel (2) did not observe any difference from the normal in their 3 patients.

Studies on the mechanism of the slow response of the tendon reflexes in myxedema have not revealed any role of the factors concerned with reflex excitation of the muscle. The slow response must be caused by an abnormality of the muscle itself. This could be either an increase in viscosity due to the myxedematous infiltration of the muscle as suggested by Harrell and Daniel (2) or a decrease in the rate of energy liberation in the contractile process.

SUMMARY

Graphic records of the ankle jerk (Achilles tendon reflex) have been made in 236 persons including normal subjects and patients who had various disorders.

The speed of contraction and relaxation of the muscle in the tendon reflex was related to activity of the thyroid gland. It was significantly increased in hyperthyroidism and reduced in myxedema. It was slowed beyond the range of euthyroid responses in 77 per cent of patients with myxedema. On the other hand, the responses of all of 16 persons with low basal metabolic rates without myxedema were within the normal range.

The speed of response increased parallel with the increase in basal metabolic rate in 55 patients with myxedema who were treated with desiccated thyroid and decreased parallel with the basal metabolic rate in 2 persons in whom myxedema developed following administration of radioactive iodine.

The slow response of the tendon reflex in patients with myxedema is due to abnormality of the contractile mechanism of the muscle rather than to abnormal activity of the neural elements of the reflex or of the mechanism of excitation of the muscle. It is not due to a lowered temperature of the muscle in myxedema.

The reflex response in myxedema cannot properly be called a myotonic or myotonoid reflex, since it bears no resemblance to the reflex response

in myotonia which, on the average, is significantly shorter in duration than normal.

Acknowledgments

We should like to express our appreciation to Dr. Mavis Kelsey and Dr. L. M. Eaton for their participation in the early phases of this work and to Miss Doris Haseth, Miss Marguerite Koelsche and Mrs. Janet Guy for their assistance in making many of the measurements.

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The Association for the Study of Internal Secretions

THE 1952 ANNUAL MEETING

The Thirty-fourth Annual Meeting of The Association for the Study of Internal Secretions will be held at the Palmer House, Chicago, Illinois, Thursday, Friday, and Saturday, June 5–6–7, 1952.

The Local Chairman of Arrangements is Dr. Willard O. Thompson.

All Scientific Sessions will be held in the Palmer House. The rooms in which each session will be held will be announced in the program and on the hotel bulletin board. The Annual Dinner is scheduled for Friday, June 7, at 7:30 P.M., preceded by cocktails at 6:30 P.M.

All members are urged to make hotel reservations immediately, inasmuch as the hotels expect to be filled to capacity. Make reservations directly with the Palmer House, advising time of arrival and departure date. Make your reservations now and avoid disappointment.

Those wishing to present papers, which will be limited to ten minutes, should send four copies of the title and abstract to the Vice-President, Dr. Evelyn Anderson, National Institutes of Health, Bethesda 14, Maryland, not later than *March 1, 1952. It is imperative that the abstracts be informative and complete with results and conclusions in order that they may be of reference value and suitable for printing in the program and journals of the Association.* The following regulations for the preparation of abstracts and titles must be carefully followed to insure consideration of the paper for the program:

1. Abstracts may not exceed two hundred words, or equivalent space, exclusive of title. No footnotes or acknowledgments to sponsors can be published. References, if used, must be placed in the body of the text. The abstract should consist of a single paragraph, if possible. Structural chemical formulas cannot be used.
2. The title heading must be arranged as follows:
   Line 1. Title, not to exceed fifteen words.
   Line 2. Author/s. The name of each nonmember-author collaborating with member-authors is to be followed by the phrase

"(by invitation)." Names of nonmembers who are introduced, *i.e.*, who are not collaborators with member-authors, are to be followed by the phrase "(introduced by . . .)." The principal degree, *e.g.*, M.D., of each author should be given after his name.

Line 3. Institution of origin and city in which institution is located.

3. The body of the abstract, typed double-space, should follow the heading. The original copy should be on bond paper. There should be three copies.
4. Abstracts should be letter-perfect, since there will be no opportunity for proofreading by authors.

1952 AWARDS AND FELLOWSHIPS

Fellowships

THE SCHERING FELLOWSHIP IN ENDOCRINOLOGY

This Fellowship will not be awarded in 1952, so that it may accumulate toward a $5,000 Fellowship to be awarded in 1953.

THE AYERST, McKENNA AND HARRISON FELLOWSHIP

The Ayerst, McKenna and Harrison Fellowship was first awarded in 1947 to Dr. Samuel Dvoskin and in 1948 to Dr. Ernest M. Brown, Jr. Dr. Brown was re-elected for the Fellowship in 1949. The 1950 Award was made to Dr. Lawrence E. Shulman.

Association Fellowships are designed to assist men or women of exceptional promise in their progress toward a scientific career in endocrinology. Fellowships may be awarded to an individual who possesses the Ph.D. or M.D. degree or to a candidate for either of these degrees. The stipend, which will not exceed $5,000, may be divided into two Fellowships in varying amounts in accordance with the qualifications of the appointee. The Committee will, in reviewing the proposed program of study, consider the amount of time which the Fellow intends to spend in course work and/or teaching. He must present evidence of scientific ability as attested by studies completed or in progress and/or the recommendation of responsible individuals. He must submit a program of proposed study, indicate one or more institutions where the proposed program will be followed, and submit statements of approval from the investigators with whom he proposes to conduct his research. He must serve full time if awarded a Fellowship. A small amount of time (10 to 15 per cent) may be allotted for course work or for participation in teaching, the latter purely on a voluntary basis.

Awards

THE E. R. SQUIBB AND SONS AWARD

The E. R. Squibb & Sons Award of $1,000 was established in 1939, and was given first in 1940 to Dr. George W. Corner; in 1941 to Dr. Philip E. Smith; in 1942 to Dr. Fred C. Koch; in 1944 to Dr. E. A. Doisy; in 1945 to Dr. E. C. Kendall; in 1946 to Dr. Carl G. Hartman; in 1947 to Drs. Carl F. and Gerty T. Cori; in 1948 to Dr. Fuller Albright; in 1949 to Dr. Herbert M. Evans; in 1950 to Dr. C. N. H. Long; and in 1951 to Dr. J. B. Collip. In 1943 no award was given. A special committee of five members of the Association selects the recipient from among investigators in the United States or Canada, on the basis of outstanding contributions to endocrinology.

THE CIBA AWARD

The Ciba Award, to recognize the meritorious accomplishment of an investigator not more than thirty-five years of age in the field of clinical or pre-clinical endocrinology, was established in 1942, but no recipient was selected in 1942 or 1943. In 1944 the award was presented to Dr. E. B. Astwood; in 1945 to Dr. Jane A. Russell; in 1946 to Dr. Martin M. Hoffman; in 1947 to Dr. Choh Hao Li; in 1948 to Dr. Carl Heller; in 1949 to Dr. George Sayers; in 1950 to Dr. Oscar M. Hechter; and in 1951 to Dr. Albert Segaloff. The Award is for $1,200. If, within twenty-four months of the date of the Award, the recipient should choose to use it toward further study in a laboratory other than that in which he is at present working, it will be increased to $1,800.

Nominations

Each member has the privilege of making one nomination for each Fellowship or Award. A nomination should be accompanied by a statement of the importance of the nominee's contributions to, or interest in, endocrinology and by a bibliography of the nominee's most important publications, with reprints if possible. The nominations should be made on special application forms which may be obtained from the Secretary, Dr. Henry H. Turner, 1200 North Walker Street, Oklahoma City 3, Oklahoma, and returned to him *not later than March 1, 1952.*

ENDOCRINOLOGY INDEX

The Association for the Study of Internal Secretions has undertaken to prepare a comprehensive Index of the articles published in *Endocrinology*. This Index will appear in three volumes. Volume III, covering papers published in 1940 through June, 1947, in volumes 26–40 of the journal, has been completed and is now available for distribution. Volumes I and II of the Index have not yet been completed.

Volume III of the Index is available gratis to members of the Association for the Study of Internal Secretions. The price to all nonmembers is $2.50. Inquiries and orders should be addressed to:

Dr. H. H. Turner, Secretary
1200 North Walker Street
Oklahoma City 3, Oklahoma.

The American Goiter Association

THE 1952 ANNUAL MEETING

The next Annual Meeting of the American Goiter Association will be held in St. Louis, Missouri, May 1, 2 and 3, 1952, at the Hotel Chase. All those who plan to attend are urged to make hotel reservations immediately.

RECIPIENTS OF VAN METER PRIZE AWARD FOR 1951

The Van Meter Prize for 1951 was awarded to *Dr. I. N. Rosenberg* of the New England Center Hospital, Boston, for his essay on "Column Chromatography of Thyroid Gland Hydrolysates."

Dr. Rosenberg was born in Boston in 1919. He was graduated from Harvard College in 1940 and from Harvard Medical School in 1943. After an interneship at the Boston City Hospital, he spent somewhat more than two years in the Army of the United States, serving as Captain in the Medical Corps. Subsequently a half-year period of work in the Department of Biological Chemistry at the Harvard Medical School was followed by a two-year appointment as Assistant Resident and Resident Physician on the Fifth and Sixth Medical Services at the Boston City Hospital. From 1949 to 1951 he was a Research Fellow, supported by the U. S. Public Health Service, in the Endocrine Laboratory of the New England Center Hospital. At present he is a Research Associate at this hospital and Assistant in Medicine at the Tufts College Medical School, Boston.

FIRST HONORABLE MENTION

First Honorable Mention was given to *Drs. Richard E. Goldsmith, John B. Stanbury and Gordon L. Brownell* of the Massachusetts General Hospital, Boston, for their essay on "The Effect of Thyrotropin on the Release of Hormone From the Human Thyroid."

Dr. Goldsmith received the A. B. degree from the University of Michigan, and the M.D. degree from the University of Cincinnati in 1945. After an interneship at the Kings County Hospital, he was a Resident at the Cincinnati General Hospital, where he subsequently had a Fellowship in Gastro-enterology. He was a Captain in the U. S. Army, serving in the 239th Station Hospital, Trinidad, and as Battalion Surgeon, 65th Infantry. Since 1949 he has been a Clinical Fellow at the Massachusetts General Hospital, Boston.

Dr. Stanbury received the A.B. degree from Duke University, Durham, N. C. in 1935 and the M.D. degree from Harvard Medical School in 1939. He was House Officer on the Medical Service, Massachusetts General Hospital in 1940–41 and was then in the Medical Department of the United States Navy from 1941 to 1945. During the period 1946 to the present, he progressed from Resident in Medicine to Chief of the Thyroid Clinic at the Massachusetts General Hospital, and from Research Fellow in Pharmacology to Associate in Medicine at the Harvard Medical School, Boston.

Dr. Brownell received the B.S. degree from Bucknell University in 1943 and the Ph.D. degree from the Massachusetts Institute of Technology, where he worked with Prof. Robley Evans on problems of radiation dosage. At present he is an Associate in Physics at the Massachusetts Institute of Technology, Cambridge, Massachusetts.

SECOND HONORABLE MENTION

Second Honorable Mention was given to *Dr. Harold P. Morris, Dr. Albert J. Dalton and Mrs. Celia S. Dubnik* of the National Cancer Institute, U. S. Public Health Service, Bethesda, Md., for their essay on "Malignant Thyroid Tumors Occurring in the Mouse After Prolonged Hormonal Imbalance During the Ingestion of Thiouracil."

Dr. Morris received the B.S. degree from the University of Minnesota in 1925, the M.S. degree from Kansas State College in 1926, and the Ph.D. degree from the University of Minnesota in 1930. Field of interest:—Nutrition and its function in the origin, growth or development of cancer.

Dr. Dalton received the B.S. degree from Wesleyan University in 1927, the M.A. degree from Harvard in 1929, and the Ph.D. degree from Harvard in 1934. Field of interest:—Experimental cytology and electron microscopy of normal and malignant cells.

Mrs. Dubnik received the B.A. degree from Hunter College in 1940. Field of interest:—Development and transplantation of thyroid tumors.

VAN METER PRIZE AWARD FOR 1952

The American Goiter Association again offers the Van Meter Prize Award of three hundred dollars and two Honorable Mentions for the best essays submitted concerning original work on problems related to the thyroid gland. Providing essays of sufficient merit are presented in competition, the Award will be made at the annual meeting of the Association which will be held in Saint Louis, Missouri, May 1, 2 and 3, 1952.

The competing essays may cover either clinical or research investigations; should not exceed three thousand words in length; must be presented in English; and a typewritten double-spaced copy in duplicate sent to the Corresponding Secretary, Dr. George C. Shivers, 100 East Saint Vrain Street, Colorado Springs, Colorado, *not later than March 1, 1952*. The committee, who will review the manuscripts, is composed of men well qualified to judge the merits of the competing essays.

A place will be reserved on the program of the annual meeting for presentation of the Prize Award Essay by the author, if it is possible for him to attend. The essay will be published in the annual Transactions of the Association.

BOOKS RECEIVED

Amenorrhea. By LAWRENCE M. RANDALL, M.D., and THOMAS W. MCELIN, M.D., Section on Obstetrics and Gynecology, Mayo Clinic, Rochester, Minnesota; 80 pages; 149 references; 1951. A monograph in *American Lectures in Endocrinology*, edited by WILLARD O. THOMPSON, M.D., Clinical Professor of Medicine, University of Illinois College of Medicine, Chicago. Charles C Thomas, Publisher, Springfield, Illinois. Price $2.25.

The Effect of Hormones Upon the Testis and Accessory Sex Organs. By NORRIS J. HECKEL, M.D., Clinical Professor of Urology, University of Illinois College of Medicine; Chairman, Department of Urology, Presbyterian Hospital; and Attending Urologist Ravenswood and Henrotin Hospitals, Chicago; 80 pages; 21 figures; 1951. A monograph in *American Lectures in Endocrinology*, edited by WILLARD O. THOMPSON, M.D. Charles C Thomas, Publisher, Springfield, Illinois. Price $2.25.

Goitre et pathologie thyroïdienne. By LUCIEN BRULL, Professeur de Clinique médicale à l'Université de Liège; 106 pages; several illustrations, diagrams and tables; 1951. Masson et C^{ie}, Paris. Price, 550 fr.

Hormones and Body Water. By ROBERT GAUNT, Ph.D., and JAMES H. BIRNIE, Ph.D., Department of Zoology, Syracuse University, Syracuse, N. Y.; 64 pages; 5 figures; 132 references; 1951. A monograph in *American Lectures in Physiology*, edited by ROBERT F. PITTS, M.D., Ph.D., Professor of Physiology and Biophysics, Cornell University Medical College, New York. Charles C Thomas, Publisher, Springfield, Illinois.

L'Année endocrinologique. By M. ALBEAUX-FERNET, L. BELLOT, P. BRÉANT, J. DERIBREUX, M. GÉLINET and CH. ZÉRAH; 168 pages, including figures and tables, 1951. Masson et C^{ie}, Paris. Price, 520 fr.

The Pituitary-Adrenocortical Function: ACTH, Cortisone and Related Compounds. A bibliography compiled by KARL A. BAER and MARJORY SPENCER with the assistance of PAULYNE TUREMAN and STANLEY JABLONSKI; 378 pages; 3,447 references; 1950. Army Medical Library, Washington, D. C.

Studies of Undernutrition, Wuppertal 1946–9. By Members of the Department of Experimental Medicine, Cambridge, and Associated Workers; 450 pages; 62 plates; several tables and figures; 1951. Medical Research Council Special Report Series No. 275. London: His Majesty's Stationary Office. Price 12s. 6d. net.

TRANSACTIONS OF THE AMERICAN GOITER ASSOCIATION—1950

THE scientific program for the 1950 meeting (in Houston, Texas) of the American Goiter Association was outstanding for its excellence. Consequently the papers presented in the 1950 number of the Transactions of the American Goiter Association represent the best current thought regarding the thyroid and its diseases.

The present volume records a significant portion of the advances made in recent years and includes discussions of them by scientists of many disciplines.

CONTENTS

Iodine Compounds in the Blood and Urine of Man

Basal Metabolic Rate and Plasma Cholesterol as Aids in the Clinical Study of Thyroid Disease

Clinical Determination of Protein-Bound Iodine in Plasma

Clinical Experience With the Blood Protein-Bound Iodine Determination as a Routine Procedure

An Appraisal of the Radioiodine Tracer Technic as a Clinical Procedure in the Diagnosis of Thyroid Disorders. Uptake Measurement Directly Over the Gland and a Note on the Use of Thyrotropin (T.S.H.)

The Radioiodine-Accumulating Function of the Human Thyroid Gland as a Diagnostic Test in Clinical Medicine

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